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The adaptive changes in the immediate postnatal period, with particular reference to respiration

Petter Karlberg, M.D.*

STOCKHOLM, SWEDEN

AFTER delivery, a number of the functions of the newborn infant must adapt themselves to extrauterine life. Among these functions the respiratory and circulatory adaptations must progress most rapidly. The gas exchange with the environment, essential for life, must be transformed from an interchange via the placenta during fetal life to an independent type of respiration and circulation through the lungs of the newborn infant. As observed clinically, at normal deliveries, the infant manages this by simply starting to breathe. Unfortunately, not all newborn infants pass successfully through the "shadow of the valley of the birth," as Clement Smith[1] has named this important and dangerous period of life. The cause may be several more or less interrelated factors, of which undoubtedly not all are known. For understanding of the possible pathologic courses, a knowledge of the adaptation during normal conditions is a valuable background. Even here, however, our knowledge is limited.

The aim of this article is to interpret these adaptive changes in normal full-term newborn infants within the immediate postnatal period, especially with regard to respiration

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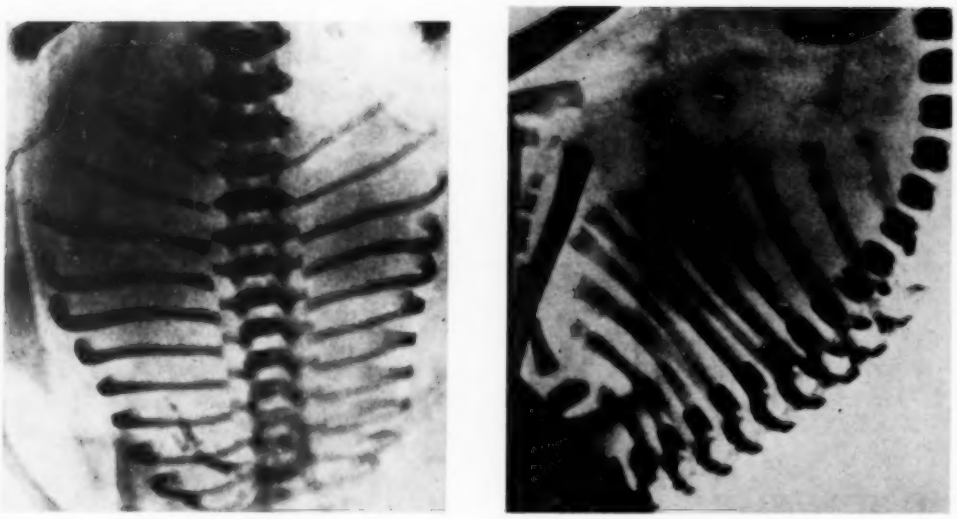
From the Pediatric Clinic, Karolinska Sjukhuset, Stockholm.

**Address, Pediatric Clinic, Karolinska Sjukhuset, Stockholm 60, Sweden.*



A *B*

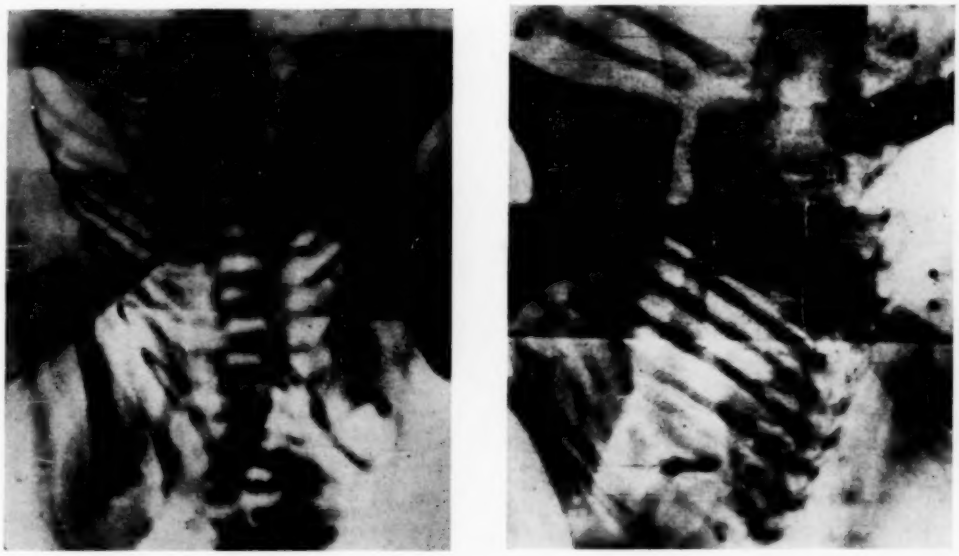
Fig. 1. Roentgenograms showing the configuration of the thorax. *A* and *B*, The intrauterine status taken in frontal and lateral planes.

in the light of present-day knowledge. For a discussion of the entire adaptive process in the newborn infant the reader is referred to the recent edition of Clement Smith's work "The Physiology of the Newborn Infant."[2]

To enable the "sleeping" fetal lungs to become active lungs where adequate gas exchange takes place the following are required: (1) aeration of the lungs, (2) establishment of adequate pulmonary circulation, (3) ventilation of the aerated lung parenchyma, and (4) diffusion of oxygen and carbon dioxide through the alveolar-capillary membranes.

One to 2 days after birth a normal newborn infant has well-established pulmonary function as judged from a great number of studies, performed mainly during the past decade; roentgenologic examinations have shown good, even aeration.[3, 4, 5] The functional residual capacity (the amount of air left in the respiratory tract at the end of normal expiration) is about 80 to 110 ml.[6, 7] Hemodynamic studies have shown well-developed pulmonary circulation with the added effect of a left-right shunt through the ductus arteriosus.[8, 9] The ventilation of the lungs during each single breath is similar to the findings in adults (the ratios, functional dead space/tidal volume, V_D/V_T, and tital volume/functional residual capacity, V_T/V_{FRC}, are equal).[10, 11] In mechanical respects each breath requires about the same increase of pulling negative intrathoracic pressure as in the adult (about 4 to 5 cm. H_2O).[12, 13, 14] There is, however, an obvious ventilatory difference. The frequency is higher in the newborn infant (30 to 40 per minute).[10] The demand on the lungs (assessed from the basal metabolic rate) in relation to their dimensions is higher in the newborn infant than in the adult. Thus the lungs must be ventilated more often.[15, 16] The effect of ventilation in regard to gas exchange, however, is the same (the ratio of oxygen consumption/minute volume, $\dot{V}_{O_2}/\dot{V}$, is of the same order).[10] The diffusion capacity[17] in relation to the demand on the function (D_{CO}/BMR) is also fairly similar.[15, 16] The same is valid also for the calculated respiratory work (work/BMR).[10]

When and how does this respiratory



C D

Fig. 1. *C* and *D*, The passage through the birth canal taken in frontal and lateral planes.[23]

adaptation occur? Considered clinically, this appears in a normal newborn infant very rapidly after delivery, at least the main part of it does. Recent studies have also shown that the immediate postnatal period is the most important one.[7, 14] The adaptive changes from the intrauterine status just prior to delivery may suitably be accounted for in 4 consecutive time periods: (1) the passage of the fetus through the birth canal, (2) the period between the delivery and the onset of the first breath, (3) the first breath and the subsequent earliest breaths, and (4) the following period to well-established lung function.

The onset of respiration in a newborn infant shows great variation. The discussion presented will be restricted to those patterns which generally are seen in spontaneous cephalic deliveries accomplished with minimal maternal sedation.

INTRAUTERINE STATUS JUST BEFORE DELIVERY

The lungs do not contain any air. The status of the lung parenchyma, especially of the alveoli, has been the subject of many studies in animals as well as in humans; the question cannot, however, be considered solved as yet.[18-22] So far there seems, in general, to have been agreement that the alveoli are not collapsed but are, to a certain extent, filled with amniotic fluid and shaped as a crumpled sac, and that an open communication is present between the alveoli and the amniotic fluid outside the fetus.

An important factor, when considering the status of the lungs, is the condition of the thorax. In roentgenologic studies of about 100 normal fetuses close to term, Borell and Fernström[23] have shown that the thorax has a similar configuration to that seen after delivery in the course of quiet respiration (Fig. 1). Thus there cannot be any extensive forces applied to the lung surfaces.

In the fetus the blood flow through the lungs is minor. Dawes[24, 25] has shown in sheep fetuses that only 12 per cent of the total cardiac output passes to the lungs. This means that the resistance in the pulmonary circulation is high in relation to the resistance in the systemic-placental circulation. Since the return from the lungs is

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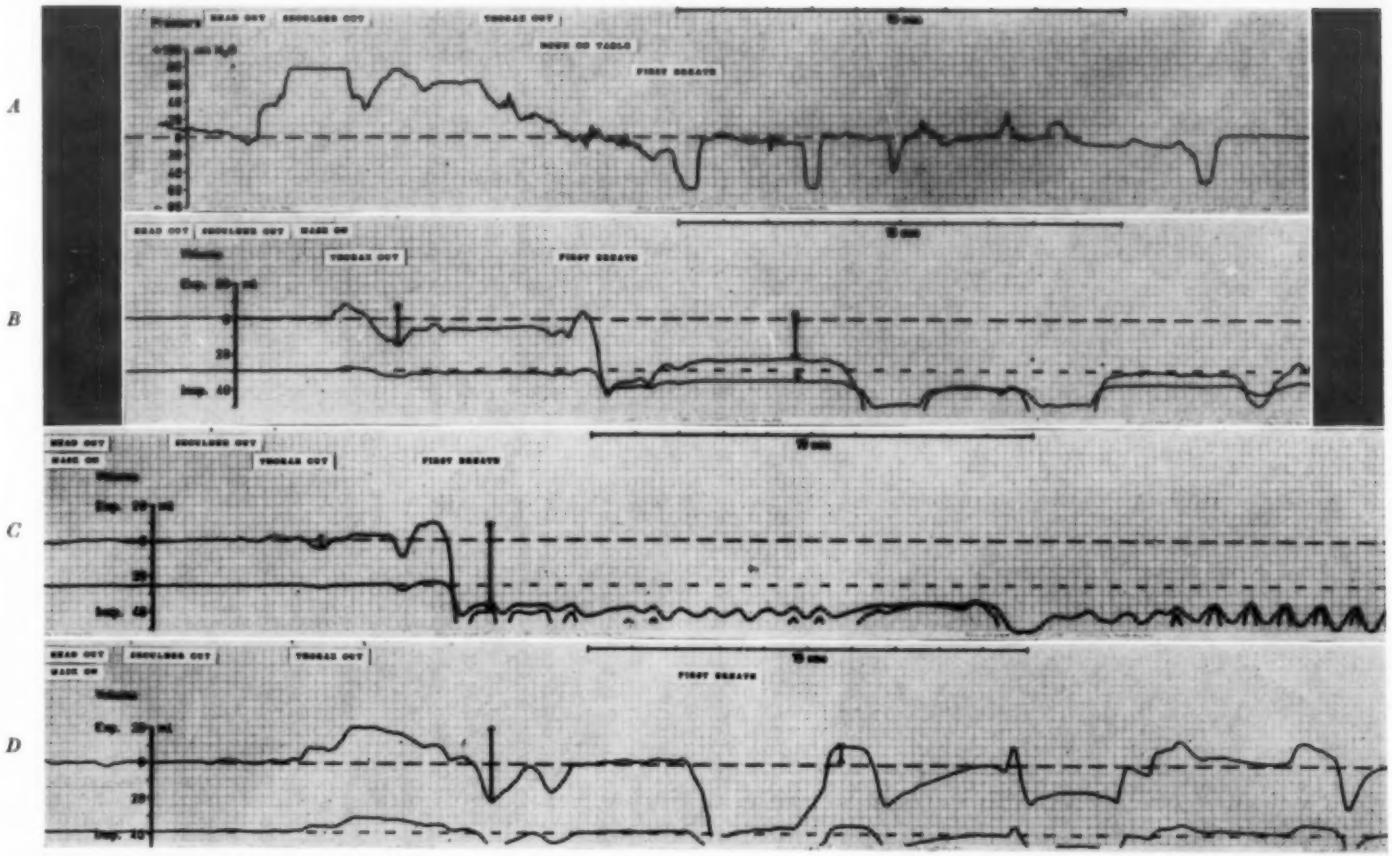

Fig. 2. *A*, Intraesophageal pressure recordings during and after delivery; *B*, *C*, and *D*, volume recordings during and after delivery. In each recording there are 2 volume curves; the lower one has a sensitivity of ¼ of the upper one to enable recording of large changes in volume. Resultant residual volumes are marked by arrows. In Case C there was a rupture of the vaginoanal septum.[33]

small, most of the blood in the left atrium is derived directly from the inferior vena cava through the foramen ovale.[26, 27] The blood is thus mainly by-passing the lungs, and both ventricles will work in parallel. In the lamb more than half of the combined flow passes to the placenta to maintain the gas exchange with the environment via the maternal blood circulation.[24, 25]

Even when the uterus is not contracted there is an intrauterine positive pressure of about 15 cm. H_2O.[28, 29] As the uterus with its contents constitutes a closed liquid system the pressure is distributed equally and it can influence neither the amount of liquid in the lungs nor the distribution of the blood between the fetus and the placenta. Thus there must be a state of equilibrium.

TIME PERIODS

The passage of the fetus through the birth canal. As early as 1918 Warnekros[30] could show by roentgenologic studies that the thorax of the fetus during its passage through the distal part of the birth canal evidently is compressed and stretched. Borell and Fernström,[23] using an improved technique on a considerably larger series of cases, have confirmed recently that there can be obvious compression (Fig. 1). They found that this compression occurs not only in the distal part but during the total passage through the birth canal. This molding of the thorax must imply a diminution in the volume of the thoracic cavity which, at least at the end of the delivery with the addition of compression of the abdomen, must cause the expulsion of a certain amount of amniotic fluid from the lungs via the upper respiratory tract. This is in agreement with clinical experience that secretions and fluid are discharged from the nose and the mouth just at the moment when the head is delivered and the thorax is still in the birth canal. The respiratory tract may be exposed so suddenly to the lower atmospheric pressure that a jet flow of fluid from the nose and the mouth is created.[31] Recording of the intrathoracic pressure, represented by the intraesophageal pressure,* has shown considerable positive pressure in the thorax.[32, 33] A typical record is shown in Fig. 2, Case A. In the cases studied, the pressure immediately and during the delivery of the body showed a range of 14 to 44 cm. H_2O and 36 to 95 cm. H_2O, respectively. In all cases the intraesophageal pressure dropped to almost zero immediately after the delivery (at least within ± 3 cm. H_2O).

At the discharge of the body of the newborn infant, the compressive forces are released and the elasticity of the thorax gives an elastic recoil of the thorax, assuming that the volume of the organs in the thoracic cavity can increase again. This is affirmed by the fall of the intrathoracic pressure which has been observed; otherwise a negative pressure should have been created. In addition, cineroentgenologic studies do not show any compression of the thorax before the first breath.[5, 7, 34] Obviously the sudden increase in volume must mean that the lungs have expanded again and have drawn the amniotic fluid backward into the respiratory tract. As some of the amniotic fluid was already expelled, air must thus be sucked in, at least into the upper part and the major bronchi of the respiratory tract.

This increase in the volume of the respiratory tract has been recorded in 5 cases by means of a mask connected to a reverse type plethysmograph and held tight to the face of the infant immediately as the head was crowning.[33] The recordings were continued during the first breaths. Fig. 2 shows 3 cases (B, C, and D) of the recordings with a change in inspiratory volume of 29, 7, and 42 ml., respectively. In Case C there was, unfortunately, a rupture of the vaginoanal septum.

The elastic recoil of the compressed thorax may thus give an inflation of air of the respiratory tract up to one fourth to one third of the expected functional residual

*Pressure was recorded by means of a water-filled open polyethylene catheter introduced through the nose to the middle of esophagus as soon as the face of the infant appeared on the perineum.

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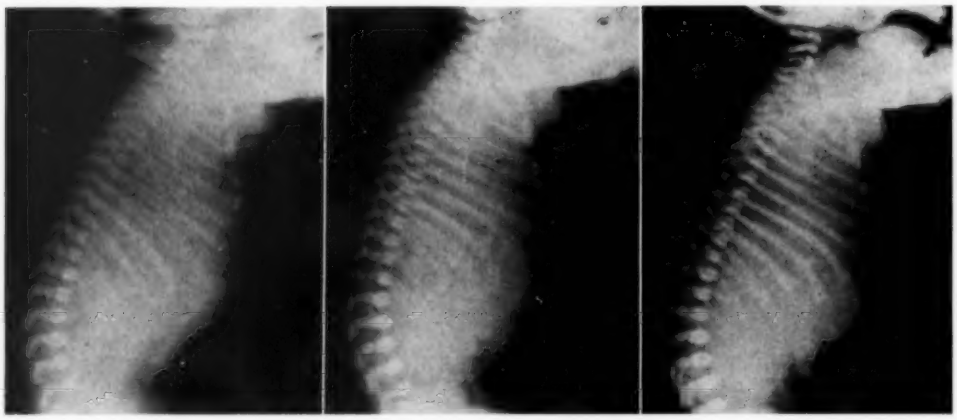


A *B* *C*

Fig. 3. Roentgenograms showing the pharyngeal motions before and during the first breath and in lateral view the aeration of the lungs during the first breath. *A*, Prior to aeration of the pharynx; *B*, 4 seconds later, only minor changes; *C*, 2 seconds later, initial air filling of the phrynx.

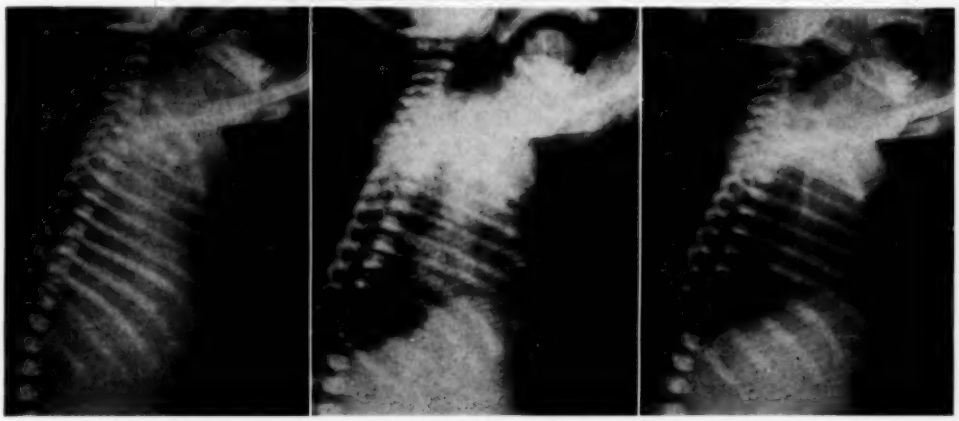
capacity at some days of age. This means a considerable contribution to the aeration of the lungs. However, there are variations.

The period between the delivery and the onset of the first breath. Experience has shown that this, in general, is a relatively short transfer period which may be of great importance in the progressive adaptation to extrauterine life. The occurrence of different mechanisms of adaptation within this period has been considered. The fact that their interpretation sometimes is contradictory can be explained by their actions during different conditions. Various situations may arise, especially if this period is prolonged as a result of many factors depending on both the course of the delivery and the condition of the newborn infant.

Before discussing these mechanisms I would like to report some of the findings from studies performed by the group in this laboratory,[7, 14, 33-37] attempting to record the changes in normal cephalic deliveries.

During this period different studies of changes in volume and changes in intraesophageal pressure overlap with respect to time. There are those which start before the delivery of the body of the newborn infant and those which start after for the purpose of studying the mechanics of breathing of the earliest breaths. Furthermore, some of these studies have been combined with recordings of pressure in the umbilical vessels. Various kinds of roentgenologic studies, some utilizing a rapid film changer, as well as cineroentgen studies have been performed.

In this period we have not recorded any appreciable negative intraesophageal pressure. This implies that the elastic recoil of the thorax is completed immediately after the delivery of the body of the newborn infant and that no remaining potential of the elastic recoil of the thorax is present, which presumably could facilitate or support the impending first breath. The recorded changes in volume have been variable. In many cases no great changes in volume have been observed. In some cases a change in inspiratory volume has been recorded with a magnitude of 5 to 10 ml., frequently followed by an expiratory phase, i.e., there was a wave-shaped change in volume. Coincident with these changes in volume a positive intraesophageal pressure wave has been recorded in cases where a simultaneous pressure recording was taken. Slow inspiratory changes in volume have been seen in a few cases. The total amount of residual volume has, in general, been fairly small, the largest amount being around 10 to 15 ml. In some of the cases studied, however,



D E F

Fig. 3. *D*, ⅓ second later, air outlining the entire oral cavity and the epipharynx and nasopharynx; *E*, ⅓ second later during the inspiration of the first breath; air present in larynx, trachea, and lungs (especially in the lower posterior parts); *F*, ⅓ second later during the expiration of the first breath; the tongue, palate, and wall of the epipharynx are in tight closure.[5]

the onset of the first breath has been preceded by a change in expiratory volume of variable magnitude (10 to 25 ml.), and simultaneously a positive pressure wave has been seen.

Some of these recorded changes in volume, particularly those with a wave pattern, are presumably the result of pharyngeal movements before the first breath, as observed by Bosma and associates[38] and Bosma and Lind.[5] Fig. 3 shows a typical set of roentgenograms from their studies. That such swallowing-like movements could be interpreted as some kind of "frog breathing" is not impossible, but hitherto the observed volume recordings have not proved that this mechanism would, in normal circumstances, result in the aeration of the lungs to any great extent before the first breath.

Another mechanism, which lately has been discussed a great deal, is the theory of lung inflation due to "capillary erection," recently put forward by Jäykkä.[39, 40] Distention of the lung capillaries with blood should erect the walls of the crumpled saclike alveoli and thus promote inflation with air. This phenomenon requires a high pressure gradient between the pulmonary artery and the lung capillaries. In this respect the sudden decline of the positive pressure toward zero inside the alveoli after the delivery may be of assistance. Avery and co-workers[41, 42] have found that vascular perfusion of excised and gas-free lungs of animals and of stillborn infants at pressures of 30 to 70 cm. H_2O is accompanied by a small reduction in the intratracheal pressure. Since this difference in pressure was less than 5 cm. H_2O, however, it seems unlikely that a "capillary erection" is by itself able to promote any considerable aeration of the lungs. In our studies in normal newborn infants we have not obtained any significant proof of the effect of this mechanism. The role of "capillary erection" under abnormal conditions where widely altered circumstances evidently are possible might be different. This is outside the limits of the present discussion, however.

During this short period between the discharge of the infant and the first breath no dramatic adaptive changes in regard to respiration seem to occur under normal conditions, even when some changes in volume, both inspiratory and expiratory, of the respiratory tract obviously are present. These can be interpreted as being due to a discharge of amniotic fluid and movement of air. This would be an addition to the possible aeration of the respiratory tract due

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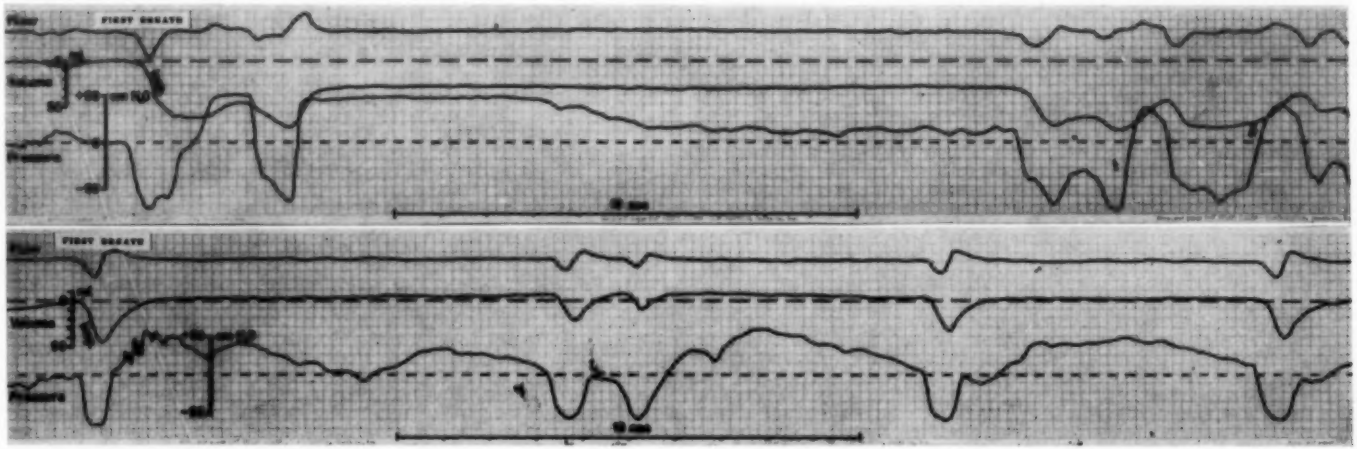
A



B

Fig. 4. Two records of simultaneously recorded volume and changes in intraesophageal pressure before, during, and after the first breaths. In *A* (Case E), there is a residual volume recorded from the first breath. In *B* (Case F), there is none.[36]

to the elastic recoil of the thorax immediately after the delivery or a substitute for failure of the first mechanism to operate. Roentgenologic studies have shown the presence of air in the upper part of the respiratory tract at this time (Fig. 3).[5, 38] Any real aeration of the lung parenchyma at this period probably is not typical. However, the sum of these preparatory mechanisms, which brings air closer to the alveoli before the first breath, appears to vary considerably even in normal cases.

Circulation is still of a fetal type as shown by the results of studies in animals.[43, 44] Lind has confirmed this angiocardiographically on a full-term newborn infant with respect to the ductus venosus and foramen ovale.[26] Presumably the same is true for the ductus arteriosus as well. If any important circulatory changes occur prior to the first breath, they have not been demonstrated.

This period between the delivery and the first breath covers a fairly orderly part of the adaptation while waiting for the first breath. There are, however, several pieces of evidence indicating that during this period delicate adaptive mechanisms may play an important role, especially if the first breath is delayed.

The first breath and the following earliest breaths. The first breath has a distinct, short inspiratory phase but a more prolonged and varying expiratory one.

Inspiration. In 15 normal deliveries, where the first breath has been recorded, there was a rapid, forceful change in inspiratory volume.[34, 36] When simultaneous pressure recordings were performed, these changes in volume were always found to be combined with a strong negative intrathoracic pressure, indicating that the first breath is a result of the expanding thoracic cage (Fig. 4). (Thoracic cage is used here to denote all the walls of the thoracic cavity, the ribs, the intercostal muscles, and the diaphragm.) This phenomenon has also been shown by cineroentgenographic studies, where a marked contraction of the diaphragm which pulls air into the lungs, is seen.[7, 34] Often this pulling is so strong that the lateral walls of the thorax present a concave shape, especially during the first part of the inspiration. Fig. 5 shows a set of typical roentgenograms. Fig. 6 illustrates, for each case, the magnitude of the recorded negative intraesophageal pressure change and corresponding inspiratory volume change, i.e., roughly speaking, the relationship between pulling intrathoracic pressure and resultant lung expansion. The inspiratory volume of the first breath is in the range of 20 to 75 ml., in most cases considerably more than the 15 to 20 ml. of resting tidal volume in newborn infants during established respiration.[10] However, the first breaths do not reach the later vital capacity, equal to the volume of a maximal cry, which usually ranges from 130 to 160 ml.[45] The change in volume in relation to the corresponding driving pressure showed large variations. It may be concluded, however, that the changes in pressure that were observed were often higher than generally expected, since they ranged from 10 to 70 cm. H_2O.

If the tidal volume of the first breath is compared with the functional residual capacity during well-established pulmonary function at an age of 1 to 2 days, i.e., 80 to 110 ml., it is evident that the first breath must imply a reasonable aeration of the lung parenchyma. This corresponds well with the results of the roentgenologic studies (Figs. 3 and 5).

To produce such aeration the pulling forces of the expanding thoracic cage must overcome various counteracting forces in the lungs. These forces are of three different kinds[35]: (1) the friction of flow of air and liquid in the respiratory tract, (2) the increase in elastic tension of the lung tissue itself, and (3) surface tension at the air-fluid interfaces in the respiratory tract.

In comparison with the normally aerated lungs of later life, the frictional forces are higher mainly as a result of narrow passageways and of the amniotic fluid which has a higher density than air and must be moved, but at the initiation of the first breath the surface tension has the greater influence.

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A *B* *C*

Fig. 5. Roentgenograms showing in anteroposterior view the status of the lungs and the thorax before and during the first breath. *A*, Before the first breath; *B*, ⅔ second later during the inspiration of the first breath (note the concave shape of the thorax); *C*, ⅔ second later at the end of the inspiration of the first breath.

D *E* *F*

Fig. 5. *D*, 3 seconds later at the end of the expiration of the first breath; *E*, ⅓ second later during the inspiration of the second breath; *F*, ⅓ second later at the end of the inspiration of the second breath.[7]

Generally speaking, the force created by the surface tension over a curved air-fluid interface operates so as to minimize the area of the surface and is related inversely to the radius of the curved surface.* When air is now sucked (or pushed) into the fluid-filled small ducts and alveoli, the influence of the surface tension thus becomes greatest at the beginning. An "opening pressure" is required. Studies of lungs of stillborn infants also have shown that a higher pressure is required for inflation with air than with fluid (about 15 to 35 cm. H_2O).[46, 47] Avery and Mead[48] have calculated that the surface tension provides a pressure difference of 26 cm. H_2O over the interface in an air bubble with the dimensions of an alveolus (radius = 40μ) in plasma. Thus the "opening pressure" theoretically ought to be of greater magnitude.

In accordance with these theoretic conclusions, studies of the mechanics of breathing (performed by simultaneously recording the changes in volume and changes in intraesophageal pressure) during the first breath, have shown that, in general, an inflation of any magnitude will take place only after a negative intrathoracic pressure of 20 to 40 cm. H_2O has been created. Following this

*In accordance with the La Place formula, $P = 2\ T/r$, where P is the pressure across the wall of the sphere; T is surface tension, and r is the radius of the sphere.

the inflation will accelerate very rapidly. This course agrees well with the findings of the cineroentgen studies of the first breaths. These studies also show the importance of the weakness of the thorax in relation to the pulling force of the diaphragm, as evidenced by the fact that aeration, caused by the first breath's inspiration, is most pronounced in the lower posterior parts of the lungs (Figs. 3, *E* and 3, *F*).

The magnitude of the increase in elastic tension of the lung tissue is difficult to assess. The studies of the mechanical factors indicate high elastic tension. Whether this is a result of general "stiffness" of the parenchyma or uneven extension of parenchyma with partial overextension is difficult to determine. It is a striking roentgenologic finding, however, that, irrespective of increasing aeration toward the lower part of the lungs, the expansion is distributed evenly rather than unevenly.

Expiration. A pause at the end of inspiration is seldom observed, so the decelerating change in inspiratory volume proceeds smoothly into an expiratory one. In spite of this, the intrathoracic pressure (intraesophageal pressure) in most cases is converted rapidly to a strongly positive one, i.e., there is an active expiration. The expiration will, in general, proceed slowly and irregularly (Figs. 2 and 4, Cases B, C, and E). Frequently a new, short inspiratory phase will appear which is of considerably less magnitude than the first one and which is followed by a new expiratory phase. In many cases the first seconds after the first inspiration are characterized by a series of expiratory phases with short, relatively small inspiratory components. The most presumptive cause for the impaired expiration, even at a high positive intrathoracic pressure, is an obstruction in the upper respiratory tract. This appears to correspond to the rhythmical pharynx-larynx closure during the first breaths, rotengenologically shown by Bosma and Lind (Fig. 3, *F*). In this way this mechanism will prevent an egress of air from the lungs and may, during the phase of high positive pressure, facilitate further

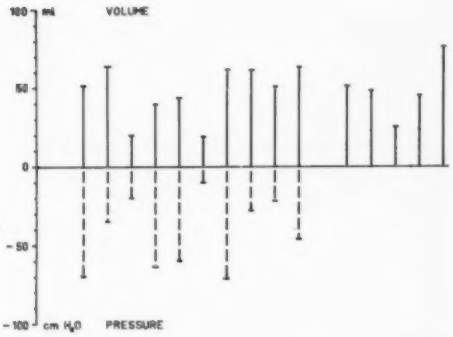
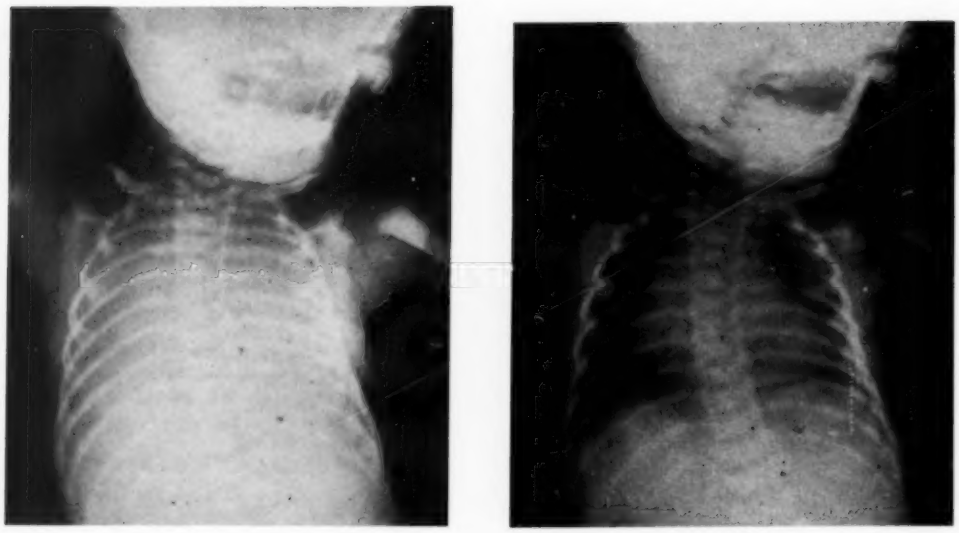


Fig. 6. A schematic diagram of recorded tidal volume of the first breath and corresponding intraesophageal pressure changes when present.

distribution of air within the lung. In some instances, the expiration of the first breath has occurred fairly rapidly and has been well delimited, succeeded by an expiratory pause (Fig. 2, Case F). This is also in accordance with Bosma and Lind's observations, as not all the cases showed a closure.

Residual volume. The result of the first breath with respect to inflation of the lungs, i.e., the residual volume, has been recorded as being quite variable in the 15 clinically apparently normal cases studied. The residual volume in 6 cases ranged from 50 to 20 ml. and in another 5 from 20 to 0 ml. In the remaining 4 cases no residual volume was recorded and the lung volume recorded actually was decreased by an amount up to 9 ml. Comparison of these findings with the changes in volume recorded before the first breath (Fig. 2, Cases B, C, and D) showed that there seemed to be an inverse relationship between the residual volume of the first breath and the residual volume resulting from the elastic recoil of the squeezed thorax and possibly in addition from the pharyngeal motions.

The subsequent earliest breaths. With respect to the tidal volume and changes in total pressure required, the following distinct breaths often failed to show any great difference except that no considerable increase in the residual volume was recorded. The cineroentgen studies show in general, however, a progressively slight increase in aera-



A *B*

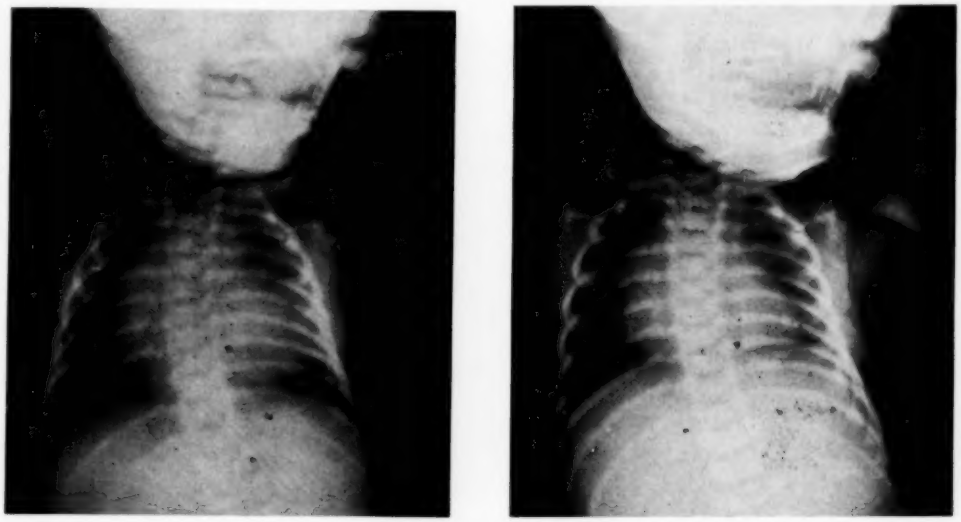
Fig. 7. Roentgenograms showing an easy and rapid first breath. *A*, Before the first breath; *B*, ⅓ second later during the inspiration of the first breath.

tion, especially in the upper parts of the lungs.

Regarding the mechanics of breathing, the volume and pressure relationships showed a lesser demand for a high initial negative pulling pressure of the following breaths compared to the first breath.

The total inspiratory respiratory work. The total work required for each inspiration was calculated from the respiratory loops obtained and constructed from simultaneous volume and pressure recordings. If we assume that the work is related to the square of the tidal volume, the degree of inspiratory effort can be estimated. When we compared the first breath and the 2 following ones we were unable to show that the inspiration of the first breath would require significantly larger *total* respiratory work than the following ones. On the other hand, since such calculated work is the sum of work required for overcoming friction from the flow of air and liquid in the respiratory tract, increased elastic tension of the lung tissue as well as collapsing forces created by surface tension, the relationships between the different components may vary between breaths. Certainly they do so, as the "opening pressure" seems to be greatest for the first breath. Also, the calculated work only reflects the work produced by the pulling thoracic cage.

In a few cases the total work calculated for the first breath was less than for the following ones. In these cases the volume-pressure relationships were such during the first inspiration that, compared with loops obtained later in life, very little frictional resistance could be present. An explanation of this unexpected finding might be the presence of lung expanding forces within the lung tissue itself as a result of circulatory changes or a positive pressure created in the upper respiratory tract. Such forces will not influence directly the intraesophageal pressure during an active inspiration since the intraesophageal pressure only represents pressure differences between the pulling thoracic cage and the pleural surface. The presence of such a phenomenon may be indicated by the fact that these cases also differed in another respect, i.e., shortly before the onset of the first breath a change in expiratory volume of 24 to 32 ml. was recorded. Further investigations are required in order to obtain an adequate understanding of these findings, but they have been reported in this article to call attention to the fact that not



C D

Fig. 7. *C*, ⅓ second later during the expiration of the first breath; *D*, ⅓ second later at the end of the first breath.[36]

in all clinically normal cases do the mechanics of the first breath fit into the pattern as implied above. Roentgenologic studies also have provided evidence that in some cases the first breath may be easy and rapid (Fig. 7).

Circulatory adaptation during the first breaths. It has been observed from animal studies that, in connection with the inflation of the lungs, there is a pronounced increase in pulmonary circulation.[25] As the ductus arteriosus is still open, resulting in a communication between the pulmonary artery and the aorta, any increase in the pulmonary blood flow requires a decreased resistance in the pulmonary circulation below the level in the systemic circulation. From experiments in lambs it has been shown that it is the expansion of the alveoli with a gas which results in the decrease in resistance in the pulmonary circulation and not the expansion of the alveoli per se, as expansion with a liquid results in increased resistance.[25] Thus the surface tension on the walls of the gas-inflated alveoli must be an important factor. The created forces which tend to collapse the alveolar wall should widen the capillaries between the alveoli. The flow of blood to the lungs during the first breaths will also be affected by considerable changes in the intrathoracic pressure. The high negative pressure during inspiration would tend to cause an increase in the flow to the lungs. The high positive pressure during expiration would tend to impede the flow to the lungs. Lind,[26] by means of angiocardiographic studies, has shown that this circulatory adaptation occurs. The blood, which is transported during the first minutes after the delivery from the placenta to the newborn infant, is probably redistributed largely in the lungs. At least a relative state of circulatory equilibrium must be established within some minutes after birth, and the neonatal type of circulation is brought into operation. Evidence for this is the pink color of the upper as well as the lower part of the normal newborn infant's body shortly after birth. For the most part circulatory adaptation seems to be initiated by the first adequate aeration of the alveoli.

Investigations to date have shown the following:

1. Interpretation of roentgenologic findings. The inspiration of the first breath

produces a drastic inflation of the lung parenchyma. This inflation diminishes during the first expiration, but a considerable amount of air remains. During the subsequent breaths a successive increase in this amount is usually seen, or an approximately steady state is apparent. In a few cases there is virtually no air remaining at the end of each breath and the following aeration thus proceeds more slowly. In general, no significant change in the configuration of thorax is seen at the end of each expiration, at least not in the anteroposterior view, which means that a change in the lung expansion is related chiefly to a change in the level of the diaphragm.

2. Interpretation of volume recordings. The inspiration of the first breath consists of one third to one half (sometimes more) of the predicted end expiratory volume at well-established pulmonary function at an age of 1 to 2 days. The net gain recorded with the inflation of the first breath varies considerably from 50 ml. to 0. In a few cases there is also a slightly decreased volume. The subsequent breaths show a relatively constant end expiratory volume.

It is noted that by means of the technique used, it is the sum of gas and liquid in the respiratory tract which has been determined. A transport of amniotic fluid from, for example, the alveoli to the upper respiratory tract does not produce any change in volume. A displacement of liquid from the respiratory tract to other parts of the body produces a decreased volume, which does not imply diminished aeration. A recorded constant volume can imply a combination of resorption and of increased aeration which counterbalance each other.

3. Interpretation of studies of mechanics of breathing. A pronounced negative intrathoracic "opening pressure" is required for the initial first breath in most cases. In the subsequent breaths this phenomenon is less marked. The *total* inspiratory respiratory work compared with the ventilatory effect acquired generally shows no consistent differences between the first 3 breaths. Diminished work at the first breath has, however, been recorded in some cases. A change in expiratory volume before the first breath was recorded in those cases.

The transition to well-established lung function. Clinical experience has shown that a normal newborn infant has an adequate respiratory function shortly after birth. The ventilation during the first 20 seconds after the onset of the first breath was calculated in the series of newborn infants studied.[15, 36] Most infants showed a ventilation of 400 to 600 ml. per 20 seconds, which means 2 to 3 times that of a resting infant a few days of age. James's[49, 50, 51] blood gas studies from birth to 1 hour of age prove that the ventilation even with regard to gas exchange is effective within some minutes of age. Already at 10 minutes of age the blood gases definitely have begun to approach the values which are considered normal later on. The oxygen consumption and the carbon dioxide output have been determined in some resting normal newborn infants repeatedly from 4 to 10 minutes of age and upward and were found to be decreasing, which indicated early a good capacity of gas exchange through the lungs.[52]

At the age of a few minutes, when the respiration as clinically seen is considered quiet, the ventilation in regard to the mechanics of breathing is similar to that found later during the neonàtal period, with the exception that the lung compliance is lower (about 2.5 ml. per centimeter H_2O, range 1.5 to 3.5, compared to 5 to 6 ml. per centimeter H_2O at a few days of age.[14, 53] This measurement tells how "compliant" the lungs are for a certain pressure change, i.e., an expression of the elastic properties of the lungs. However, this includes the size of the lungs as well. Normal lungs show a good correlation between the lung compliance and the functional residual capacity from newborn infants of a few days of age to adulthood. In the longitudinal study of a group of newborn infants from birth to 1 week of age, the lung compliance showed a hyperbolic increase with age. There was a good agreement between the lung compliance observed

and direct measurements of the functional residual capacity from ½ to 1 hour of age on.[7] This increase in lung compliance coincides with the decrease in heart volume found during this time period.[54] The lung compliance in quiet breathing periods at some minutes of age may be used as an indicator of the aeration of the newborn infant's lungs, at which period no direct measurements are as yet available. From such calculations a full-term, healthy newborn infant of this age would be expected to have a functional residual capacity of about 50 to 70 ml.

At least half of the adaptive respiratory changes for extrauterine life, assessed from the degree of aeration of the lungs, seem to take place prior to a few minutes of age in a normal newborn infant; the subsequent changes occur at a less rapid rate. Thus it seems reasonable to limit the discussion of the respiratory adaptive changes to a postnatal period of 1 to 2 minutes.

DISCUSSION

In this outline of the adaptive changes within the immediate postnatal period only those with spontaneous cephalic deliveries with a rapid, alert onset of breathing have been included. The cause for the onset of breathing will not be discussed here.

The aeration of the lungs is the key to the respiratory adaptation. With regard to the volume of air used for aeration, the first breath is the main means of transport of air into the alveoli. At the end of the first breath there will be a certain amount of air left and a residual volume created. The squeezing of the thorax during delivery with a drainage of amniotic fluid and the resultant elastic recoil of the thorax with aeration of at least the upper part of the respiratory tract must be valuable preparation for the first breath. This is indicated by the observation that the more this preparation seems to have been performed the less is the recorded residual volume of the first breath. The sum of these two kinds of residual volume has been found to range from 35 to 60 ml. Taking into consideration a functional residual capacity of 50 to 70 ml. at a few minutes of age, predicted from the lung compliance, the continued aeration after the first breath will proceed at a fairly slow rate. This will fit with the findings that no considerable further increase in residual volume from the second and subsequent breaths has been recorded.

However, there are some contradictions in this proposition. Since the elastic recoil of the thorax is completed immediately after the delivery, different recorded residual volumes of the first breath should result from correspondingly different expansions of the thoracic cage. Since roentgenologic studies show a similar configuration of the thorax in utero immediately after birth and after the first breath, different volumes of the thoracic cage will mean chiefly different resting levels of the diaphragm.

Hypothesis. During the expiration of the first breath, a very high intrathoracic pressure, presumably caused by pharyngeal-laryngeal closure, generally is recorded. This may be a basis for a rapid resorption of amniotic fluid into the lung capillaries during the first expiration. Under such conditions a change in expiratory volume of the respiratory tract would take place without being detected by the volume recording system used. On the other hand, with good drainage of amniotic fluid during the delivery, there will be less amniotic fluid for resorption and the expiratory decrease of the lungs will be recorded as a regular change in expiratory volume, i.e., less difference in the recorded volume of the respiratory tract at the start of the first breath than at the end.

The possibility of aeration of the lungs by "frog breathing" (Bosma and Lind) and "capillary erection" (Jäykkä) must be included in this discussion. It would not seem likely that these mechanisms would contribute to any great extent to the aeration of the alveoli before the first breath of the normal newborn infant, even though they may have a preparatory effect, particularly the pharyngeal activity observed. Some assistance in creating a residual volume with the first breaths seems possible. Definite proof is not yet available, however. Their possible importance in pathologic states is

not relevant to this discussion. Further studies need to be done, especially with combined techniques, for a better evaluation of the above-mentioned mechanisms.

The dynamics of the individual freshly aerated alveolus. Recent studies on a specific surface-tension-acting lining material on the walls of the alveoli have increased remarkably our understanding of the stability of the volume of aerated alveoli.[55-58] Avery and Mead[48] have shown that the lining material is present in the lungs of full-term infants and in stillborn infants close to term. This starts to act when an air-fluid interface is created on the walls of the alveoli. Its specific characteristic is low surface tension upon compression but increased surface tension on extension. The difference in surface tension at the extremes of these states is about 10 times. At maximal extension the surface tension is about the same magnitude as that of various body fluids and other tissues.

The surface tension on the concave internal surfaces of an alveolus tends to make the surface smaller, i.e., to promote collapse of the alveolus. The alveolus is prevented from collapsing by the elasticity of the surrounding tissues. If the surface tension remains constant and then the collapsing forces increase with a diminishing radius of the alveolus, the collapsing forces should be of the greatest magnitude in the small alveoli and of the smallest magnitude in the large alveoli. This would imply that with different-sized alveoli, all connected to the same airway, the smaller, more sharply curved ones should tend to empty their contents into the larger, and the distribution of air should be more uneven, some alveoli completely collapsing. With this specific surface-acting material present, however, an automatic balancing of the volume between the aerated alveoli will take place.

In a newborn infant there must, evidently, be a critical transfer period just at aeration. Before aeration the elastic forces in the lung tissues and the thoracic cage are acting alone and they keep the alveoli expanded to a certain extent. During the beginning of the first breath, when an air-fluid interface is created in the alveoli, the collapsing force must be strong. There are sharply curved surfaces in a liquid with a high surface tension ("opening pressure"). With increasing "air bubble" in the alveoli, the collapsing force will decrease (less curved surface). If the air-fluid interface reaches the alveolar wall with its lining material, the collapsing force will not increase again during the subsequent expiration in spite of a return to more curved alveolar surfaces since the surface tension will decrease because of the lining material. Furthermore, if an alveolus is not completely aerated, the "air bubble" will stick to the walls and the fluid will enter the alveoli first.

Hypothesis. If resorption of the amniotic fluid in partly inflated alveoli should take place during the expiration, the specific surface-acting material lining the alveolar walls would be reached more rapidly by the air-fluid interface.

It is evident that this mechanism is an extremely important factor in obtaining evenly distributed aeration of the alveoli and in ensuring stability. It is shown by Avery and Mead's findings that this lining material is lacking in premature infants with birth weights below 1,200 grams and in newborn infants with developed hyaline membranes who definitively are in greater risk of atelectasis.

The dynamics of the total number of aerated alveoli. Even if there is low surface tension in the aerated alveoli at the end of an expiration, counterbalancing forces are required to inhibit a collapse. With well-established pulmonary function the functional residual capacity of the lungs, i.e., the amount of air in the respiratory tract at the end of a normal expiration, is adjusted by the balance between the expanding thoracic cage and the contracting lung tissue. This means that the volume of the thoracic cavity must be important. Roentgenologic studies show the resting configuration of the thorax to be relatively unchanged throughout the entire adaptive period, so that the main change in the volume of the thoracic cavity will be caused by altered

levels of the diaphragm. At post-mortem examinations the diaphragm generally is found at the third intercostal space in stillborn infants without pathologic changes in the lungs and in newborn infants with widespread atelectasis; it is found at the fourth and fifth spaces in newborn infants who have died without atelectasis.[59] Thus the volume of the thoracic cavity does not seem to be the primary adjuster of the total aeration of the lungs. In roentgenologic studies of living newborn infants, a lower position at the eighth space is seen at the end of normal expiration.[60] The aeration of the lungs must involve a change of the elastic properties of the lung tissue. The created air-fluid interface in the alveoli, however, can act only in a collapsing direction.

The circulatory changes may be of importance here. The great increase in the amount of blood in the lung capillaries, which is produced during the inspiration of the first breath, may serve as a kind of structural support for the walls of the alveoli during the succeeding expiration. At compression of the blood-filled capillary net around the alveoli, forces are created to prevent collapse.

Hypothesis. During the first breaths especially this possible mechanism may be pronounced. Since this requires a large blood flow to the lungs, a decreased blood flow to the lungs during the inspiration of a forceful first breath could diminish the amount of resultant residual volume, i.e., the subsequent breaths would also require a high initial negative intrathoracic pressure ("opening pressure"). Support for this hypothesis has been obtained from the studies of the mechanics of breathing at the onset of respiration.[36]

In a lusty full-term newborn infant the cord ruptured just at the end of the delivery. The blood flow from the placenta had thus already ceased before the elastic recoil of the thorax occurred. The first breath was missed at the recording, but the constructed respiratory loops from the next 4 breaths all had the shape of a typical first breath, i.e., an "opening pressure" seemed to be required for each breath. These findings were in agreement with the very forceful retraction of the chest during each inspiration which was observed clinically.

The report by Avery and co-workers[41] that a small reduction in the intratracheal pressure is produced by vascular perfusion of excised and gas-free lungs of animals and of stillborn infants is of great interest. Even though the aim of their study was to investigate the possibilities of lung expansion due to a "capillary erection" mechanism, i.e., a mechanism which is different from the one discussed here, their findings indicate that at a certain pressure blood-filled lung vessels are able to create a force tending to expand the alveoli.

The aeration of the alveoli with the interrelated increased filling of the pulmonary capillary bed will give an increased lung volume. As pointed out above, there is evidence which indicates that a certain portion of this increased lung volume is balanced mechanically within the lungs by a change in the elastic properties of the lung tissue. The level of the diaphragm is adjusted so that at the end of normal expiration the thoracic cavity is given a volume which, balanced with a corresponding lung volume, will give a slight negative intrapleural pressure. This adjustment of the diaphragm must be influenced greatly by the interrelated respiratory and circulatory adaptive changes initiated.

The circulatory adaptation. The basis for adequate lung function requires, in addition to aeration of the alveoli, complete functional rearrangement of the circulatory system. From the discussion above it is evident that the circulatory adaptation is related intimately to the respiratory one. There seems to be enough evidence available to conclude that the main circulatory adaptive changes are induced by the onset of breathing. It is thus evident that factors disturbing the circulatory adaptation may also interfere with the respiratory one.

In infants delivered by cesarean section, for example, there is no preparation for the first breath by the squeeze of the thorax. In addition there is a markedly diminished blood flow from the placenta to the infant after the delivery and, in general, slow initiation of respiration. It is a well-known

clinical observation that within the first minutes the skin of these infants is often pink in the upper part of the body in contrast to a more or less cyanotic lower part. With improving respiration the cyanosis will disappear. This phenomenon can be explained by a slow, progressively decreasing resistance in the pulmonary circulation, resulting in a period when the venous blood from the right ventricle partly goes to the lungs for gas exchange and partly directly to the descending aorta via the ductus arteriosus. With increased aeration of the lungs the resistance will decrease sufficiently to give a neonatal type of circulation with a left to right shunt through the ductus.

In normal newborn infants good aeration of the lungs and well-established pulmonary circulation are present within a few minutes after birth. Whether some circulatory factors are acting to prepare the conditions for the first breaths in normal newborn infants has not yet been shown convincingly.

Ventilation and gas exchange in the immediate postnatal period. A normal newborn infant seems to be capable of producing good ventilation with the first breath in respect to the volume of air moved per unit of time. Studies of the mechanics of breathing within the first minutes of life have not shown any remarkable increase in total inspiratory work in relation to gained inspiratory volume when compared with periods of crying respiration in normal newborn infants a few days of age.[53]

Within a few minutes after birth the gas exchange between the pulmonary capillary blood and the alveoli has reached such a capacity that the blood gases begin to approach the levels found later in the first week of life. During the first days of extrauterine life, however, the arterial blood shows a somewhat lower partial pressure of oxygen and a somewhat higher partial pressure of carbon dioxide compared with corresponding values in adults.[61, 62] The explanation for these findings is under discussion. They may indicate a slightly impaired capacity of the oxygen diffusion which to some extent is compensated for by hyperventilation.

Even though this discussion has been limited to the condition of a normal, alert newborn infant's immediate adaptation to extrauterine life, which seems clinically simple, our knowledge of these phenomena is remarkably incomplete. Any tendency toward abnormal conditions will increase the complexity of the newborn infant's adaptation. Further studies in this field, which could result in greater understanding of these functions, would increase our ability to help more effectively distressed newborn infants as they pass through the "shadow of the valley of the birth."

SUMMARY

An outline of the adaptive changes in the immediate postnatal period with particular reference to respiration is given. Only the conditions at normal spontaneous cephalic deliveries have been discussed. The period of time has been limited to 1 to 2 minutes after the delivery as at least half of the adaptive changes seem to have begun within that time. The remainder progress in a decelerating fashion and continue up to some days of age. The key change in the respiratory adaptation to extrauterine life is the aeration of the lungs. Inspiration of the first breath seems to be the main contribution to the aeration of the alveoli; however, there are several possible supporting mechanisms. The need of further studies in this field is emphasized.

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Circulatory factors in relation to idiopathic respiratory distress (hyaline membrane disease) in the newborn

Clement A. Smith, M.D.*

BOSTON, MASS.

ANYTHING one says about hyaline membrane disease in these times of so much research activity must be taken as tentative. Certainly anything one writes must be so tentative as to be best left unprinted, for the ideas on which it is based (if not too old to be without current interest) are usually so new as to be merely medical gossip or, if beyond that stage, may well be already in the hands of some other editor.

Even among the facts, some selection is necessary if any coherent story is to emerge. We seem to have almost too much rather than too little information about this subject of "idiopathic respiratory distress" or hyaline membrane formation in newborn babies. The difficulty is fitting the information neatly together. I have, therefore, chosen to focus mainly on circulation and circulatory factors about which so much has been learned in the last few years and months. This omits a good deal from present consideration. It leaves out the recent evidence of reduced or absent activation of plasminogen in tissues of infants dying of hyaline membrane formation[1] whose cells thus appear to lack one step in the process leading to the lysis of fibrin. Concentration on circulation also omits the fascinating difference in surface-tension properties shown by Avery and Mead[2] to distinguish lungs of infants with hyaline membranes from those of other infants and adults. The omission of these new developments from further consideration here is not because we know them to be any less important in respiratory distress than is circulation but because circulation has been more widely studied and discussed and its disturbances, once we are sure they are fundamental to the problem, may be dealt with by several therapeutic approaches.

There is activity in still other fields either too recent or incompletely explored to be summed up clearly as yet. These include the chemical or metabolic status of infants who have or are likely to develop respiratory distress, and the general reflex or au-

From the Department of Pediatrics, Harvard Medical School, and the Boston Lying-in Hospital.

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**Address, Boston Lying-in Hospital, 221 Longwood Avenue, Boston 15, Mass.*

tonomic nervous system responses of such infants. The former aspects are being investigated most actively by Usher,[3] James,[4] and Reardon,[5] and the latter by Desmond and her colleagues[6] at Baylor. Both approaches are promising; neither has yet reached the stage of being tested widely or confirmed by other workers or even by further investigations which the authors referred to are themselves continuing.

The idea that respiratory distress originates in some disturbance of circulatory adjustment following birth goes back at least to 1955.[7] On the basis of considerably less evidence than has since become available, Lendrum[7] argued that "clinical and pathological findings in the newborn premature infant who dies of 'pulmonary hyaline membrane disease' . . . [could be] . . . interpreted as manifestations of left heart failure." Not long thereafter came the demonstration by Gitlin and Craig[8] that the substance of the hyaline membrane is largely fibrin and their postulation that the process begins as an effusion of plasma, with its normal component of fibrinogen, from pulmonary circulation. Although Gitlin and Craig avoided any suggestion as to how the effusion arose and left a role for aspirated amniotic fluid as a thromboplastic agent, their investigation rather definitely ruled out the former prevailing theory that the protein of the membranes originated in amniotic fluid which was aspirated during birth. In the following year, 1957, Gitlin did write that he was "inclined to the opinion that the effusion may be accounted for on the basis of left ventricular failure, possibly due to sudden increase in peripheral resistance encountered when the umbilical cord is tied off."[9]

During these developments, a great deal of basic information on the circulation at and immediately after birth in another mammal was presented by Geoffrey Dawes and his associates in England. Of several demonstrations published in rapid succession from Dawes' laboratory, the most impressive to many readers was that by Born, Dawes, Mott, and Widdicombe[10] which proved temporary patency of the ductus arteriosus, with a left-to-right flow of blood through it, as a normal occurrence for at least some hours after delivery of the sheep fetus. The concept of this as a "neonatal" circulation in contrast to the fetal and the adult circulations and, for its brief interval, as normal as the other two was an interesting and novel possibility not previously considered in the prevailing opinion that the ductus must normally close at birth.

Interesting as was the behavior of the ductus in the lamb, it seemed unlikely for two reasons that a similar type of neonatal circulation occurred normally in the human infant. A "ductus murmur" had not been heard in the newborn period. Moreover, even though the ductus was patent, whatever blood might pass through it appeared likely to go from the right to left as it had done before birth, and, as Eldridge and Hultgren[11] demonstrated, must occur (at least under some circumstances) by their comparisons of the oxygenation of blood from the upper and lower extremities of newborn infants. But when, in March of 1957, Adams and Lind[12] published the results of cardiac catheterization of 8 normal newborn infants, 3 of the 8 did appear to have had shunts through the ductus like that described as normal in the newborn lamb, even though no ductus murmur could be heard in any of the infants. Adams and Lind not only showed that, at least in some normal infants, the ductus might temporarily be open but they may have done an even more significant service by setting a precedent for further investigations by cardiac catheterization in the newborn period.

A few months later, James and Rowe[13] added more evidence, obtained by catheterization, that the ductus might normally be patent in newborn infants in the absence of audible murmurs. Evidence was also offered which indicated that the response of the infant to hypoxia in the newborn period might be a fall in systemic blood pressure below that in the lungs so that blood from the right heart might temporarily revert to the fetal pattern and avoid the lungs by passing through both the foramen ovale and the

open ductus. The possibility of such an event offered further testimony to the patency of the ductus in neonatal life and to the reversible direction of blood flow which could produce another large variable in a circulation whose channels were themselves changing.

Another means of investigating the heart and great vessels had been employed by Prec and Cassels.[14] They had, in 1955, introduced carefully timed injections of dye into a peripheral vein and then recorded photoelectrically the wave of rising and falling concentration as the dye arrived at another peripheral point after its passage through the heart and lungs. Such curves of dye dilution are not precise quantitative data but their shape can and does give indications that a shunt has allowed some of the injected dye to avoid the route of the normal circulation of the adult. Actually, the curves obtained by Prec and Cassels indicated that in most of the newborn infants studied, some dye, and therefore some blood, was passing from the aorta to the pulmonary artery through the ductus arteriosus, as in the neonatal circulation of the lamb, while, in some infants, the dye dilution indicated a flow of blood in either direction through the ductus at different phases of the cardiac cycle.

By this time there was abundant evidence that the circulation of the newborn infant is not the relatively fixed arrangement which had formerly been generally accepted but a dynamic and shifting system of pressures and flows through vessels, at least one of which could not only remain open as a holdover from fetal life but could even reopen after temporary postnatal closure. Since no one had as yet reported any murmurs in relation to the evidences of ductus patency, great interest was roused when Burnard did so in 1959.[15]

Burnard's contribution was a rare one in medicine. The enthusiastic report of a positive finding, later quietly abandoned when several subsequent investigators fail to confirm it, is frequent enough. But the announcement of a positive finding obtained by a persistent searcher after numerous other workers have obtained negative results is much less common. In any case. Dr. Burnard not only heard but recorded by phonocardiography a crescendo systolic murmur in 37 per cent of the normal infants he examined within a few hours after birth. The site and other aspects of this murmur led him to conclude that it originated from the flow of blood through the ductus arteriosus from the aorta to the pulmonary artery.[15]

Several other observations related to the circulation have been reported by Burnard.[16] Some were concerned directly with the murmur. Obviously, quiet and concentration were needed to hear it. It was heard most commonly within the first 3 hours after birth and seldom after the seventh hour. In infants examined during the first 15 minutes, asphyxia of a mild degree was accompanied more commonly by a murmur than was the prompt onset of breathing.[16] Normal premature infants, breathing normally, had the same rather large incidence of ductus murmurs as did term infants with asphyxia; in premature infants with dyspnea or "breathlessness" (by which the author apparently meant the respiratory distress most commonly caused by hyaline membrane formation) the murmur was especially common. "Reduction in rectal temperature seemed to result in amelioration of dyspnea and disappearance of the murmur. Conversely, warming 3 babies shortly after birth brought about dyspnea as well as the murmur. The suggestion is made that the murmur probably means an increase in flow through the ductus arteriosus above the rate present after normal birth."[16]

One must go at length into Burnard's work as an important but as yet a unique investigation. So far as I know, no one else has approached his record for picking up these sounds, even after he indicated that they were present. Indeed, anyone who has tried to listen to the heart of a small, rapidly breathing premature infant in respiratory distress must admire not only Burnard's skill but also his persistence. We have not done

nearly so well in our hospital, probably because we have not persisted so patiently.

With all the evidence that a unique sort of circulation normally occurs during the brief time at which one often sees respiratory distress in living infants (and finds hyaline membranes in their lungs if they die) and with so many clues which indicate that congestive failure of the left heart (or some other disturbance of circulation) might be the cause of transudation of plasma into the pulmonary air spaces, Nadas and Rudolph, at the Children's Hospital, decided with us at the Lying-in Hospital that some more direct investigation than had yet been made here urgently was indicated. Especially in premature infants and in those born to diabetic women, the threat of respiratory distress was so large and the attempts we and others had made to treat it had been of such dubious value, that we clearly needed the information available only from a fresh approach. The most direct approach possible appeared to be by the earliest possible use of catheterization, a technique whose reasonable safety was apparent from the large experience of our colleagues from the Children's Hospital.

After approximately 18 months, during which investigations of varying degrees of completeness were carried out by the catheterization of more than 30 newborn infants, the records of the 24 most complete studies were analyzed for significant differences between the circulation of normal infants and those with mild and severe respiratory distress. The data were presented in two brief reports to the Society for Pediatric Research[17, 18] in May, 1959; the catheterization findings are now being prepared for detailed publication by Rudolph. The results and their interpretations were clear in some respects but puzzling in others. There appeared to have been large left-to-right shunts in severe respiratory distress and a much smaller shunt, or none at all, in infants with mild or no distress. Had there been unequivocal cardiac failure in those infants who had large left-to-right shunts, with relative overwork of the left ventricle, a much higher left auricular pressure would have been expected in them than is apparent in Table I. At the present stage of this investigation, Rudolph and Nadas feel that cardiac failure has not been proved.

A more striking and originally unanticipated departure from the findings at catheterization in the normal infants was the relatively reduced presssure in pulmonary and systemic vessels found in practically every infant with severe respiratory distress. A similar reduction of pulmonary blood pressure in infants with hyaline membranes has not been reported by other workers but few, if any, other catheterization studies have been done on a group of similar infants.

There have been, however, at least two fairly extensive investigations of systemic blood pressure in newborn infants, both of which have shown that respiratory distress is accompanied, indeed may be preceded, by relative reduction of peripheral arterial pressure. The data obtained by Segal and Martinek[19] are numerous and consistent. The work of Neligan[20] was carried out in our own hospital, where the peripheral blood pressure readings could be checked against those simultaneously made by Rudolph from the catheter in the aorta of infants, as discussed above. Neligan's frequently repeated measurements of blood pressure on individual infants do not lend themselves to tabulation, and the data presented to the American Pediatric Society meeting in 1959 have not yet been published. His results showed differences between the courses of immediately postnatal peripheral blood pressure in asphyxiated infants and in infants with the respiratory distress of hyaline membrane disease as compared with the blood pressure of normal newborn infants not disturbed by either of these factors. Asphyxia at birth tended to be accompanied by a temporary elevation in blood pressure, such as might normally occur as a response to asphyxia in people of any age. On the other hand, infants whose lungs showed hyaline membranes had no such elevation of blood pressure but, instead, a greater fall of sys-

Table I. Summary of hemodynamic data in normal infants and infants with respiratory distress[18]

Infants	Age (hours)	Pressure (mm. Hg)							Pulmonary–systemic flow ratio
		Left atrium minus right atrium	Pulmonary artery			Aorta			
			s.*	d.†	m.‡	s.*	d.†	m.‡	
8 normal	5 to 40	1.2	55	24	36	63	39	47	1.14:1
8 with mild respiratory distress	2 to 11	1.8	52	28	38	61	40	50	1.11:1
8 with severe respiratory distress	3 to 21	2.1	38	19	27	47	29	37	> 3:1

*s. = systolic.
†d. = diastolic.
‡m. = mean.

temic pressure than that found by the same investigator to follow normal birth. These results suggest that the infant in whose lungs the hyaline membranes are forming has begun extrauterine life without a normal vasomotor response mechanism.

Thus there is considerable evidence to indicate that respiratory distress is accompanied by left-to-right shunt through an open ductus arteriosus and by both pulmonary and systemic hypotension. Since the ductus is, after all, a blood vessel and an artery and since it has contracted insufficiently in those infants who develop respiratory distress and ductus shunt, it is possible that the failure of ductus contraction is but a single local example of a generalized vasomotor phenomenon involving not only the systolic and pulmonary arteries but also the one artery which acts as a bridge between them. An important further investigation must then be the cautious trial of those drugs known to have vasomotor activity, a study for which we now await appropriate opportunities.

Other observations and communications continue to interest us in the puzzle of how circulatory factors are related to respiratory distress. In some places the evidence is rather against than for a relationship. We surely are not alone in having seen occasional infants whose congenital abnormalities must have produced left heart failure yet who showed no membranes at autopsy. We have had no success in treating respiratory distress by means which do succeed in known heart failure, especially the use of digitalis; we may not have tried this soon enough after birth. Nor have we felt sure enough that the open ductus was the basic problem to convince ourselves that routine surgical closure of that vessel in a series of newborn premature infants was justifiable.

We have been greatly interested in Burnard's[21] latest paper in which he presents very strong evidence that cardiac dilatation is present consistently in respiratory distress. Roentgenographically, the heart size of the infants with respiratory distress studied by him was significantly increased. Our diagnostic films are probably not taken as exactly as those he obtained for his study, and our set of controls was not chosen as well. This may be why roentgenograms of many of our infants with respiratory distress do not reveal a cardiac diameter larger than that of our normal infants. Burnard's data not only indicate cardiac dilatation during respiratory distress but they also reveal that the thoracic diameter is a less variable standard of comparison than we had thought formerly. This latest paper by Burnard takes full note of the observation by Cross, Dawes, and Mott[22] that the lamb's heart at normal birth is producing about all the cardiac output of which it seems capable; thus relatively little further work might easily induce cardiac failure. We do not know that the same circumstances are true in the newborn human infant.

One disturbing consideration is the old problem of what is meant by cardiac failure. Another is the question: when does hyaline membrane disease or respiratory distress begin? I refuse to attempt a definition of cardiac failure but will assume that the kind of cardiac failure referred to by those who would thus explain hyaline membrane formation cannot be just a terminal phenomenon. If cardiac failure is to be considered a cause of respiratory distress and of pulmonary hyaline membranes, it should be present before the distress and membranes begin. And though the membranes and the distress may not be present at birth (to judge by histopathology and respiratory rates), we are more and more convinced that something is wrong with these infants in the delivery room and probably during the delivery.

Are they, then born with cardiac failure already established? We would think that unlikely. We would think cardiac failure may be a later phenomenon, perhaps frequently a terminal one, but from our observations it is not a clearly indicated or proved cause of the respiratory distress syndrome at its immediate postnatal beginning. That cause when found need not be cardiac failure but may turn out to be some other disturbance of circulation, a general vascular or vasomotor change. Until we know what it is, we watch the work of others with interest and attempt to learn more about their observations as they may be applied to cases in our own nurseries. Although the primary cause may be elsewhere, we continue to think that circulatory factors lie somewhere near the center of this puzzling and important problem.

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Ventilation and ventilatory mechanics in the newborn

Methods and results in 15 resting infants

Paul R. Swyer, M.R.C.P. (Lond.),* R. C. Reiman, and

John J. Wright, B.Sc. (Lond.)

TORONTO, ONTARIO

THE PURPOSE of this paper is to describe a method for measuring ventilation and ventilatory mechanics in newborn infants, and to present the results in 15 normal resting newborn infants.

The basic measurements are those of the respiratory air flow rate and the intraesophageal pressure change together with the respiratory rate. Various derivations of these data enable calculation of respiratory volumes, lung compliance, and combined viscous resistance to lung tissue movement and to air flow. The mechanical work expended on the lungs in respiration can also be determined.

APPARATUS

Respiratory air flow rate is measured by the pneumotachograph. This instrument was first used in physiologic studies by Fleisch[1] in 1925 and subsequently developed in different form for use in adults by J. C. Lilly.[2] In the present instrument, a stainless steel wire screen of 2.0 sq. cm. (400 mesh per square inch) is placed in the air stream, and the pressure drop across this resistance is measured. An electrical pressure transducer* measures the very small pressure drop of 0.1 mm. of water per 10 ml. flow per second. The pressure drop across the screen is directly proportional to the rate of air flow. The electrical output from the pressure transducer is fed into a galvanometer with an optical amplification system and is recorded photographically.†

The response to square wave input for the pneumotachograph shows no observable distortion.

The "dead" space of the pneumotachograph mask assembly is 8 ml. The silicone putty ring used to apply the mask to the face bulges into the mask and reduces the

From The Department of Paediatrics, University of Toronto, and The Research Institute, The Hospital for Sick Children, Toronto. Supported by a grant from the Department of National Health and Welfare.

**Address, The Research Institute, The Hospital for Sick Children, 555 University Avenue, Toronto 2, Ontario, Canada.*

*Statham strain gauge, 12401 West Olympic Blvd., Los Angeles, Calif.

†Model R. G. 6 Photo-Kymograph, Waters Corporation, Rochester, Minn.

dead space by approximately 40 per cent (Fig. 1). It is doubtful whether any remaining space within the mask is truly "dead" because of the wide and permeable pneumotachometer orifice to the outside air. No systematic acceleration in respiratory rate has been observed during the study of any infant; rather the rate tended to decrease with prolonged rest. Since the infant's respiratory rate rose significantly with an increase of 0.5 per cent in the concentration of inhaled CO_2,[3] it was concluded that the dead space in the face assembly had a negligible effect.

Intraesophageal pressure as a reflection of intrathoracic pressure is simultaneously recorded through a 1.19 mm. internal diameter water-filled polyethylene catheter (No. 8 Fr. feeding catheter) introduced 10.5 cm. from the external nares to the level of the third thoracic vertebra. A differential pressure strain gauge transducer is again used to convert pressure to a proportional electrical output which is fed into a galvanometer optical amplifying system, similar to that used for the pneumotachograph. The interior of the face assembly is connected to the second port of this strain gauge so that the transpulmonary pressure is measured. The compliance of this water-filled strain gauge system was 0.0008 ml. per centimeter of water. The response to a square wave input was 70 per cent at 0.06 seconds, and the natural frequency was 3 to 4 cycles per second. Provided respiration had approximately a sine wave form, it was calculated to be adequate at a respiratory rate of approximately 40 per minute. However, in practice, a cyclical artefact interfered with the estimation of dynamic pressure changes,* although its effect on static end tidal pressure was small, especially as 20 to 30 breaths were averaged.

Later, infants were studied with an intraesophageal air-filled balloon-strain gauge system which had improved response characteristics and was capable of reflecting more accurately the higher frequency components likely to be encountered with intraesophageal pressure changes. These have been reported to be of the order of 10 cycles per second.[4] The compliance of this balloon system was 0.006 ml. per centimeter of water. The response to a square wave input was 70 per cent at 0.05 second without visible natural resonance.

The balloon was made, with size modification, according to the directions of Mead and his associates.[4] It was 5 cm. long, and the tip was passed 16 cm. from the anterior nares so that the balloon rested in the thoracic esophagus.

Calibration of the pneumotachometer is

*For this reason, separate measurements for viscous resistance and per cent elastic work in Cases 7, 10a, 15, 19, 27, and 32 in Table I are not given.

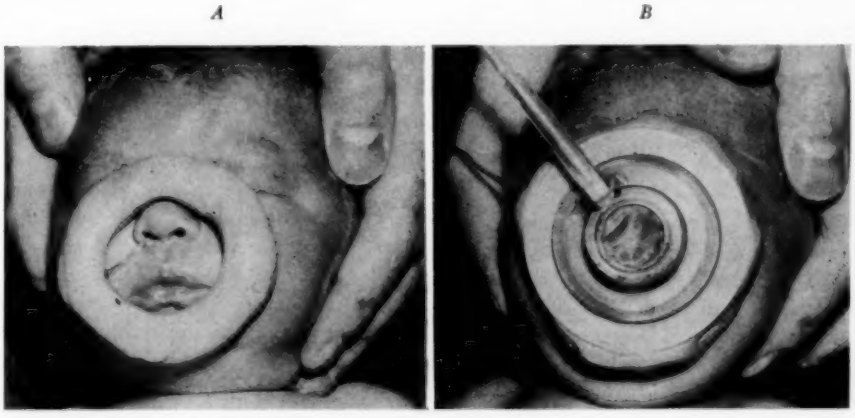

Fig. 1. *A*, Silicone putty ring and intraesophageal catheter in position. *B*, Pneumotachometer in position.

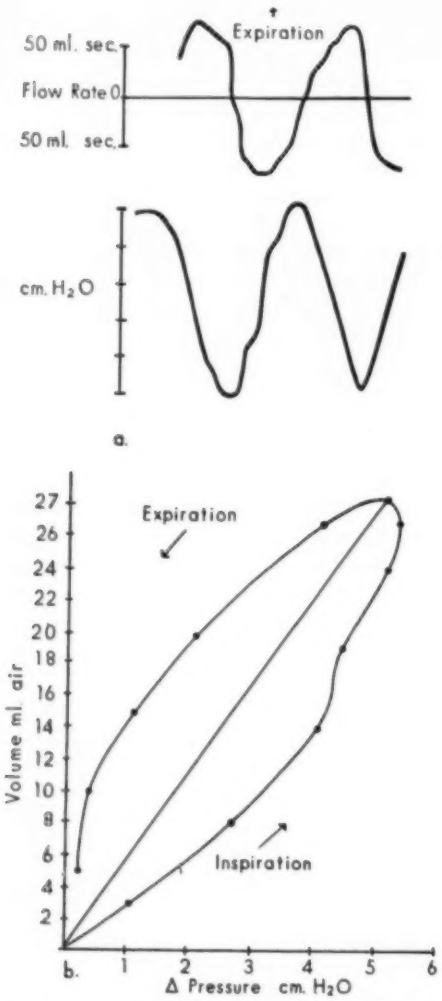

Fig. 2. *A*, Normal pneumotachogram *(upper trace)* and intraesophageal (transpulmonary) pressure trace. Infant aged 36 hours. Weight, 2.75 kilograms. *B*, Pressure volume diagram constructed from this breath.

carried out with a Tri-flat flowmeter.* Deflection is a linear function of flow rate from 0 to 170 ml. per second. The intraesophageal pressure channel is calibrated against a water manometer. Only pressure change, not absolute pressure, is measured. Calibrations are carried out for both esophageal and pneumotachometric pressure channels immediately after each study.

Twenty to thirty breaths are analyzed from each study and the results averaged.

*Model G9145B., Manostat Corp. 20-26 N. Morre St., New York 13, N. Y.

PROCEDURE

The infant is restrained in a supine position by a method that does not impede chest movement. The intraesophageal catheter or balloon is passed into the esophagus through the mouth or nose. A ring of silicone putty is applied to the face and the flanged part of the pneumotachometer rested upon it. Owing to the viscous, elastic, and adhesive properties of the putty, an airtight seal is formed through which the intraesophageal catheter is led (Fig. 1).

THEORETICAL CONSIDERATIONS

The basic measurements obtained are airflow rate and transpulmonary pressure changes. From these data, ventilatory volume, viscous lung resistance, lung compliance, and the work of breathing may be calculated.

Fig. 2, *A* shows a typical tracing. The intraesophageal pressure and air-flow rate can be read directly from the calibration. Volumes are derived by integrating the area enclosed by the flow rate curve and the base line of the pneumotachograph with a planimeter. The mean of a series of 20 consecutive measurements of one area was found to be 26.2 ml. with a standard deviation of 1.6 ml. This error in volume measurement is comparable to that recorded for the body plethysmograph by Cross (± 10 per cent).[5]

Mead and Whittenberger[6] have pointed out that expiratory tidal volume, as measured by integration of a pneumotachogram, is approximately 107 per cent of inspiration owing to expansion of inspired gases by heat and saturation with water vapor. For this reason, inspiratory volumes alone are used in our calculations.

Minute volumes are the product of the inspiratory tidal volume and the respiratory rate per minute.

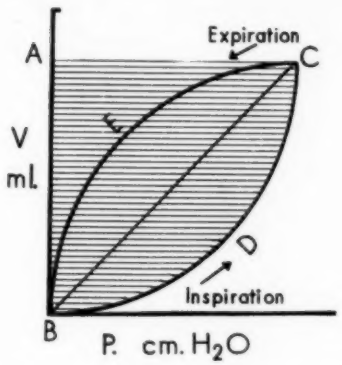

Fig. 3. Theoretical lung pressure/volume diagram. V = tidal volume change. P = tidal pressure change. *BC* = compliance line. Area *ABC* = elastic work. Area *BDC* = viscous work. Area *ABDC* = total inspiratory work. Note that the expiratory work area *BEC* is completely covered by the inspiratory elastic work area *ABC* (see text, p. 8).

The resistances to be overcome in breathing are of two types—elastic and viscous.

Elastic resistance is that opposed to inspiration by the elastic recoil of the lung and chest wall. The chest wall component is not measured by this method. If transpulmonary pressure change (P) is plotted against volume change (V) during a respiratory cycle, a pressure/volume diagram is obtained (Fig. 3). The slope of the line (*BC* in Fig. 3) joining the points of no-flow at the tidal extremes is a measure of lung elastic resistance usually expressed as the inverse relationship, compliance (V/P).

There are three components to the viscous resistance. The first is the airway resistance; the second is the frictional tissue resistance. Frictional tissue resistance has been measured separately in adults,[7, 8] but not in infants. Marshall and Dubois[7] showed it to be one sixth of the total nonelastic resistance. The third component, the resistance opposed by the inertia of air to acceleration, is negligible. By our method it is the sum of these components, the total viscous pressure, which is measured experimentally. Referring to the pressure/volume diagram in Fig. 3, the pressure difference between the static lung compliance line *(BC)* and the dynamic volume/pressure line in inspiration *(BDC)* on the abscissa represents the pressure required to overcome total viscous resistance.

In mid-inspiration, where peak air flow rates are reached (point *D*, Fig. 3), the deviation from the compliance line *(BC)* is most marked. The degree of pressure deviation (ΔP_{FR}) is a measure of the extra pressure required to overcome viscous, mainly airflow, resistance. The resistance (R) may be calculated from the flow resistive pressure (ΔP_{FR}) and the simultaneous rate of air flow ($\dot{V}$).

$$R = \frac{\Delta P_{FR}}{\dot{V}}.$$

Its value is approximately constant during quiet breathing in adults.[9] Our results suggest that this is also true for infants (Figs. 4 and 5). Therefore, flow resistive pressure (ΔP_{FR}) and rate of air flow ($\dot{V}$) bear an approximately linear relationship during quiet breathing. Fig. 4 shows a graph constructed from the tracing shown in Fig. 2 illustrating this relationship.

Artefacts may interfere with the accuracy and phasing of pressure/volume recording; of these, pressure components consequent on the cardiac cycle, changes in esophageal muscle tone, and blockage of the esophageal catheter with mucus are the most important. Fortunately, all of these are fairly easily recognizable on the tracing, and such records can be discarded.

The mechanical work done on the lungs in breathing is most accurately calculated by construction of a pressure/volume diagram (Fig. 3) which has the graphic dimensions of work. The triangular area *ABC* is equivalent to purely elastic work and is mathematically represented by 0.5 PV (where P = pressure difference and V = volume change between points of no flow at the tidal extremes), and the ellipse *BDC* is equivalent to viscous work. The sum of the two areas represents the total inspiratory work per breath.

Table I. Results in 15 cases

Case	*Sex*	*Age*	*Wt. (Kg.)*	*Resp. rate (per min.) f.*	*Tidal vol. (ml.) V_T*	*Av. max. esophageal pressure (cm. H_2O) difference*	*Compliance (ml./cm. H_2O)*
12	F	2 hr.	3.49	34	24.6	5.7	4.5
34	F	4 hr.	2.3	42	14.5	2.6	5.7
32	M	6 hr.	3.12	32	20	7.9	2.9
19	M	10 hr.	3.46	48	15.6	4.1	4.3
10a	F	18 hr.	3.46	50	12.3	3.6	3.4
22	F	1 da.	3.18	32	26	4.9	5.2
27	F	1 da.	2.5	30	16.3	5.5	3.3
46	M	2 da.	2.86	31	31.5	6.1	5.0
33	M	3 da.	2.41	50	17	2.4	7.1
10b	F	3 da.	3.29	40	19.7	3.6	5.3
59	F	3 da.	2.98	40	23	6.6	4.8
15	F	4 da.	3.96	30	27.3	6.1	4.9
7	F	9 da.	3.18	36	18.9	4.9	4.5
42	F	9 da.	2.46	24	23.9	3.8	6.4
31	F	11 da.	2.38	32	18.1	4.7	5.6
Average			3.0	36.7	20.6	4.8	4.9

*N.K. = Not known, due to recording artefacts.

In quiet breathing, expiration is passive because of elastic recoil of the lung. The energy required (*BEC* in Fig. 3) is covered by that stored in the elastic lung in inspiration (area *ABC* in Fig. 3). Energy which is not used in overcoming viscous resistance in expiration (*ABEC* in Fig. 3) is expended against continuing inspiratory tone of the respiratory muscles. This involves metabolic but no mechanical work. The total mechanical work of breathing done on the lungs is thus equivalent to inspiratory work.

McIlroy's[10] simple formula (0.6 PV) has been used to calculate work in this series. Simultaneous pressure volume diagrams in suitable cases, free from artefacts in the tracing, have confirmed the close agreement between diagrammatic and formula (0.6 PV) calculations of mechanical work demonstrated by the Boston workers.[10]

Mechanical work can be expressed in terms of physiologic (kilo) calories* if a 5 per cent mechanical efficiency is assumed for the respiratory muscles.

*One gram centimeter is equivalent to 2.3438×10^{-8} kilocalories.

MATERIAL

Fifteen normal infants were studied, ranging in age from 2 hours to 12 days. Delivery in all cases was uncomplicated. All had been asleep for 15 minutes or longer when respiration was recorded.

RESULTS

Results are shown in Table I.

The average tidal volume of the 15 resting infants was 20.6 ml. or 6.9 ml. per kilogram of body weight, and the frequency of respiration was 36.7 per minute. The minute volume was 730 ml. or 246 ml. per kilogram.

The average maximal pressure change with respiration was 4.8 cm. of water. Average compliance was 4.9 ml. per centimeter of water. The standard error of the mean of a series of 10 compliances from 1 patient was ± 0.4 ml. per centimeter of water.

The average resistance was 26 cm. of water per liter per second. The standard error of the mean of a series of ten consecutive resistances from 1 patient was ± 1.6 cm. of water.

The average work per breath per kilogram of body weight was 20 Gm. cm., while the average work per minute per kilogram of

Work/breath (Gm. cm.)	Work/min. (Gm. cm.)	Resistance (cm. H_2O/L./sec.)	Per cent elastic work	Flow rate max. inspiration (ml./sec.) $\dot{V}$	Flow rate max. expiration (ml./sec.)	Insp./exp. time ratio
80	2,720	22	62	44	39	.88
23	965	9	81	40	22.4	.48
95	3,040	N.K.*	N.K.	46	28	.79
43	2,060	N.K.	N.K.	58	43	.59
26	1,300	N.K.	N.K.	33	33	.74
79	2,520	32	76	42	30	.73
52	1,560	N.K.	N.K.	51	46	.67
97	3,000	24	69	56	49.2	.75
26.5	1,325	18	72	47	37	.79
43	1,740	28	55	45	49	.88
92	3,680	34	59	58	42	.74
96	2,022	N.K.	N.K.	70	44	.42
56	2,000	N.K.	N.K.	33	27	.82
54	1,300	17	68	65.4	38	.50
51	1,630	54	52	42	30	.95
61	2,050	26	66	48	37	.77

body weight was 688 Gm. cm. This is equivalent to 1.36 kilocalories per day or about 1 per cent of the infant's basal metabolism. The percentage of elastic work averaged 66.

The average peak inspiratory/expiratory flow rates were 48/37 ml. per second respectively. Assuming the cross-sectional area of the trachea of a newborn infant to be 0.28 sq. cm.,[13] the peak linear velocity is 172 cm. per second (3.7 m.p.h.) and 130 cm. per second (2.6 m.p.h.), respectively, for inspiration and expiration.

The pneumotachometric pattern varied with the individual, but was repetitive from breath to breath.

The inspiratory pattern tended to follow a sine wave form, but expiration showed three main forms, a "sine" wave resembling the inspiratory form (Fig. 6*A*), an "exponential" type where the flow rate tended to be an exponent of the falling flow pressure head (Fig. 6*B*), and, finally, a "changing resistance" type (Fig. 6*C*), where expiration had a more or less steady but low flow rate, consequent on a changing expiratory flow resistance, probably connected with a change in oropharyngeal posture. Occasionally, a sustained pressure in the face of a steady resistance results in a constant expiratory flow rate throughout the breath. These obstructive types of expiratory flow patterns are probably artefacts related to the fact that an intraesophageal catheter is in place in the nasopharynx. Expiration through pursed lips was often observed in such cases.

The ratio of the time of inspiration to the time of expiration averaged 0.77 at a frequency of 36.7 respirations per minute, but varied widely between 0.48 and 0.95, the lower ratios tending to occur with lower respiratory rates.

DISCUSSION

Minute volumes in this series cannot necessarily be considered as basal. Cross[5] has shown that minimal minute volumes may not be reached until the infant has been asleep for periods of 1 hour or more, whereas most of our infants were tested after 15 to 20 minutes of sleep. The minute volumes in this series have been extrapolated from measurements made over a relatively short period of time. It has frequently been observed that respiration is periodic so that

selection of relatively short periods of respiration for analysis may be misleading unless the statistical sample is large. Table II gives the average resting minute volumes obtained recently by other investigators for comparison.

Cook and co-workers[10] have pointed out the essential similarity of the known volumetric and mechanical factors involved in respiration in infants and adults. The differences depend solely on the differences in lung capacity and airway size (and hence resistance). These differences account for the theoretical calculation that, in terms of mechanical work, the most economical rate of respiration for the neonate is about 37 per minute compared with 12 to 15 per minute for the adult.[11, 12]

Mead[13a] has recently questioned this concept of regulation of optimum respiratory frequency for minimal rate of mechanical work at a given alveolar ventilation. He suggested that the optimum respiratory frequency should be that at which minimal average force was developed by the respiratory muscles, which would not ordinarily be the same as the frequency for minimal rate of respiratory work.

From experimental data on guinea pigs, he predicted frequencies for minimal average force of 81 ± 7.6 per minute, and for minimal work of 59 ± 6.3 per minute. His

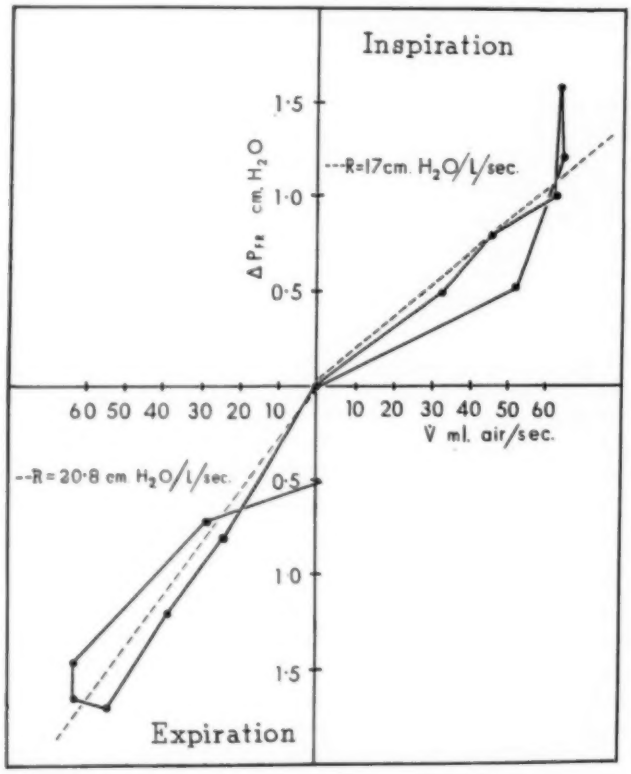

Fig. 4. Viscous resistance. Graph of successive flow resistive pressure differences (ΔP_{FR}) versus airflow rates ($\dot{V}$) during the normal inspiration/expiration in Fig. 2. The average inspiratory resistance is 17 cm. H_2O/L./sec. The average expiratory resistance is 20.8 cm. H_2O/L./sec. Infant aged 36 hours. Weight, 2.75 kilograms.

observed respiratory frequencies for the same animals conformed more closely to the minimal average force concept at 82 ± 8.5 than to the minimal work rate concept. This contrasts with data from human infants in the series of Cook[10] and our own series, as well as in adults,[11, 12] where predicted rates for minimal work corresponded closely with observed rates. Differences in mechanical efficiency of muscles may explain this discrepancy. Further data, including simultaneous mechanical work and oxygen consumption studies, are required.

The relatively minor differences between the results in the present series and the only other comparable previous study[10] can probably be accounted for by the different methods used and the relatively small number of cases studied (Table III).

McIlroy and Tomlinson[14] have also reported results of a study of the mechanics of respiration in 7 infants (Table III). The average compliance of 1.82 ml. per centimeter of water was substantially less than that found by the Boston group (5.2 ml./cm. H_2O), or in our study (4.9 ml./cm. H_2O).

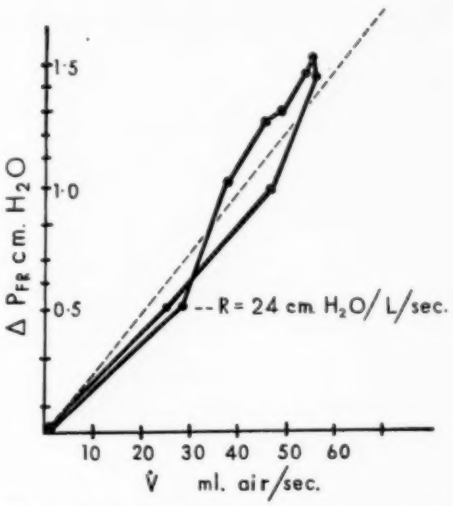

Fig. 5. Viscous resistance. Graph of successive flow resistive pressure differences (ΔP_{FR}) versus airflow rates ($\dot{V}$) for inspiration. The usual approximately linear resistance relationship is exposed. Infant aged 48 hours. Weight, 2.86 kilograms.

This explains the increased percentage of elastic work reported by them (83 per cent)

Table II. Minute ventilation and respiratory rate according to recent investigators

Author	*No. of cases studied*	*Minute volume per Kg. body wt. $\dot{V}$/Kg.*	*Resp. rate (per min.) f.*	*Method*	*Remarks*
Cross, 1949[5]	36	171	28.6	Body plethysmograph, head seal, spirometer	Quiescent for 20 min.
Howard and Bauer, 1949[15]	10	248.6	46.5	Body plethysmograph, spirometer	During sleep
Boutourline-Young and Smith, 1950[16]	17	182	39	Body plethysmograph, neck seal, pressure transduction	"Steady state," usually 20 min. asleep +
Cook and others, 1957[10]	18	203	38	Body plethysmograph, head seal, spirometer	"Quiet"
Cross, Tizard, and Trythall, 1957[17]	32	149.5	31	Body plethysmograph, head seal, spirometer	Sleep; quiescent for 20 min.
Geubelle, 1957[18]	14	265	38.1	Body, plethysmograph, neck seal, spirometer	15 min. asleep +
Stahlman, 1957[19]	44	150	47	Double Donald Christie box with mask and spirometer	"Quiet"
Present series	15	246	36.7	Pneumotachometer, integration of flow curve	15 min. asleep +

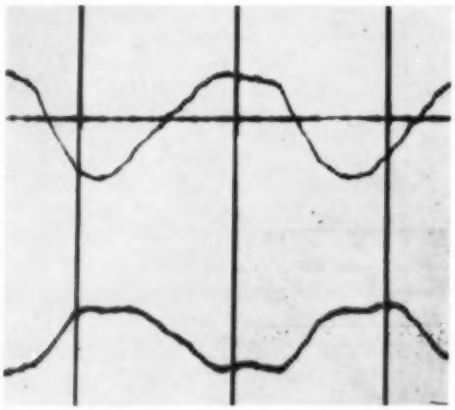

Fig. 6. In each case the upper trace is flow rate with expiration above the base line, while the lower trace is transpulmonary pressure change. A per nasal intraesophageal catheter was used. *A*, Pressure/flow rate record showing an approximate sine wave form for both inspiration and expiration. Infant aged 11 days. Weight, 2.38 kilograms.

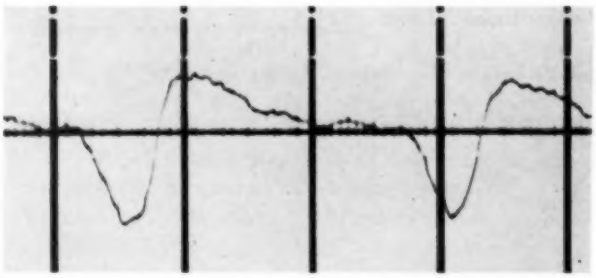

Fig. 6*B*. "Exponential" type of expiratory flow tracing where expiratory flow rate tends to be an exponent of falling flow pressure. (Flow tracing only shown.) Infant aged 9 days. Weight, 2.4 kilograms.

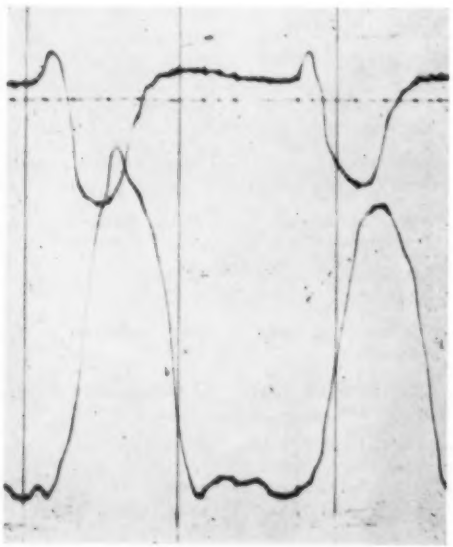

Fig. 6*C*. "Changing resistance" type where expiration had a more or less steady but low flow rate consequent on a changing expiratory flow resistance, probably connected with changing oropharyngeal posture. Infant aged 4 days. Weight, 3.96 kilograms.

Table III. Results in two recent studies of ventilatory mechanics compared with present series

Author	*No. of cases*	*Wt. (Kg.)*	*Resp./ min. f.*	*Tidal volume (ml.) V_T*	*Minute volume (ml.) $\dot{V}$*	*Esophageal pressure (cm. H_2O)*	*Compliance (ml./ cm.H_2O)*	*Work/ min. (Gm. cm.)*	*Per cent elastic work*	*Resistance (cm. H_2O/ L./sec.)*
Present series	15	3.0	36.7	20.6	730	4.8	4.9	2,050	66	26
Cook and others[10]	18	3.0	38.0	16.0	608	5.0	5.2	1,380	70	29
McIlroy and Tomlinson[14]	7	3.1	46.2	13.4	578	5.0	1.82	2,600	83*	N.K.

*Calculated from authors' data.

compared with the other two series (70 and 66 per cent, respectively. Figures for viscous resistance were not quoted by McIlroy and Tomlinson. Total respiratory work was substantially higher. This was due to the low compliance observed as well as to the fact that the infants were not in a resting state during their study.

SUMMARY

A method is described for the study of the mechanics of respiration in the newborn by measuring simultaneously the pressure in the esophagus and the air flow rate.

Figures are given for 15 normal newborn infants for tidal and minute volumes, lung compliance, airway resistance, air flow rates, and the mechanical work of breathing.

We wish to thank Dr. C. E. Snelling for his encouragement to continue this work.

Grateful acknowledgment is made to Dr. L. S. James and his associates at the Columbia Presbyterian Medical Center for providing details of the construction of the pneumotachometer used, with minor modifications, in these studies.

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Chemical thermoregulation of full-term and premature newborn infants

Gy. Mestyán, M.D., and F. Varga, M.D.

PÉCS, HUNGARY

INEFFICIENCY of thermoregulation is one of the most striking features in the newborn infant. In the usual environment the full-term infant generally maintains body temperature within the normal range while the premature infant is threatened by severe hypothermia. Some investigators emphasize the inadequacy of physical thermoregulation[1-3] or the unfavorable surface-volume ratio[4, 5]; others assume insufficiency or complete lack of chemical thermoregulation is the chief cause of so-called "initial hypothermia" in the newborn.[6-8] Mordhorst[9] observed in premature newborn infants an increase in the production of heat in a cold environment from the sixth day onward. Recently, Brück and associates[10] observed a marked increase on the first day of life following exposure to an environment of 20 to 23° C. (68 to 73.4° F.). The experiments of Brück and co-workers and the observation of Davis and associates[11] show that the increased O_2 consumption of premature infants is accompanied by increased muscular activity. In our experiments we endeavored to find answers to the following two questions:

1. Can an increase in the production of heat be observed in an environment of 20 to 22° C. (68 to 71.6° F.) in the quietly resting newborn infant?

2. What is the role and importance of muscular activity in premature and full-term infants exposed to cold?

From the Children's Clinic, University of Pécs, Hungary.

METHODS

Full-term and premature infants aged 1 to 10 days were investigated. The infant was placed half naked (in a short shirt) in an airtight metabolic chamber which was then submerged in a water bath. Heating or cooling of the water bath adjusted the temperature to or maintained it at the desired level. A glass window in the chamber permitted observation of the infant throughout the experiment. Consumption of O_2 and production of CO_2 were measured continuously with the Kipp-Noyons diaferometer and body temperature by means of a thermocouple inserted about 10 cm. into the rectum. The behavior and activity of the infant were carefully observed. In most cases the experiments were started in an environment of 20 to 22° C. (68 to 71.6° F.), with the temperature being raised later to 30 to 33° C. (86 to 91.4° F.), and subsequently cooled to 21 to 22° C. (69.8 to 71.6° F.).

RESULTS

In the experiment demonstrated in Fig. 1 the alert infant was rather quiet at first in

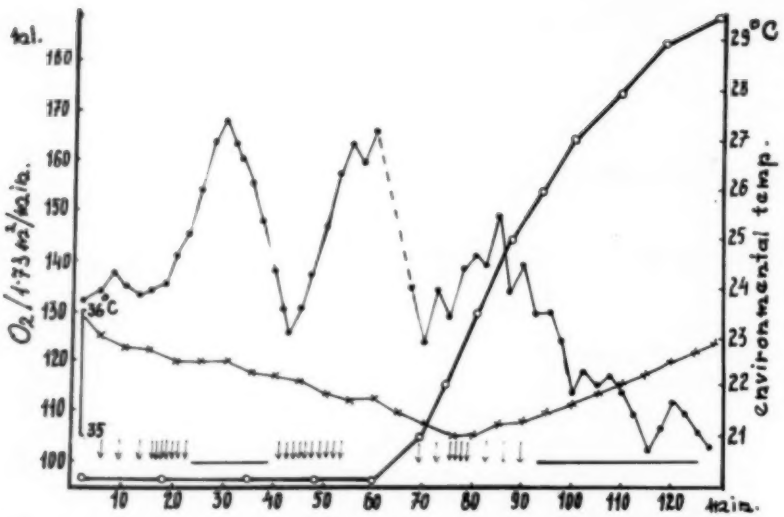

Fig. 1. Full-term infant. Age, 4 days; weight, 2,750 grams (6 pounds, 1 ounce). ●——● = O_2 consumption; ×——× = body temperature; ○——○ = environmental temperature; ↓↓ = restlessness; —— = asleep.

an environment of 20° C. (68° F.), and O_2 consumption is fairly stable. During this period the rectal temperature decreased 0.3° C. (0.6° F.). Thereafter the infant became increasingly restless; O_2 consumption increased, and the rectal temperature did not decline further. Soon after this, the infant fell asleep; O_2 consumption gradually returned to the basal level, and the rectal temperature decreased again. After a few minutes, sleep was interrupted by our gradually increasing restlessness until the infant cried. The rate of O_2 consumption and the rectal temperature were the same as in the preceding period of restlessness. Thereafter the environmental temperature was raised and, at 26° C. (78.8° F.), the infant became quiet and slept during the remaining time of the experiment. Parallel with the increasing environmental temperature, the body temperature increased and O_2 consumption fell below the initial level.

Fig. 2 demonstrates that the O_2 consumption of a sleeping infant at 22° C. (71.6° F.) did not differ from that of an infant in the more usual environment of 30° to 33° C. (86° to 91.4° F.). In a few minutes the infant awakened and became progressively restless, and at times muscular twitching was observed. Muscular activity resulted in a considerable elevation in the metabolic rate, and concurrently the rectal temperature ceased to fall. During warming, activity decreased gradually, and, when the baby fell asleep, the energy metabolism returned to the basal level.

Fig. 3 demonstrates an experiment with a mature infant at 3 days of age. In the warm environment, the sleeping infant consumed O_2 at a steady rate. In the course of cooling, at an environmental temperature of 26° C. (78.8° F.), the rectal temperature began to decline, the infant began to awaken and moved slightly. At 23° C. (73.4° F.) restlessnes and O_2 consumption increased markedly. Thereafter, parallel with warming of the environment, the activity diminished and the infant fell asleep. Body temperature after a slight initial fall was practically unchanged throughout the experiment.

Fig. 4 demonstrates an experiment on a premature infant at 1 day of age. After a short initial sleep the infant bec ne increas-

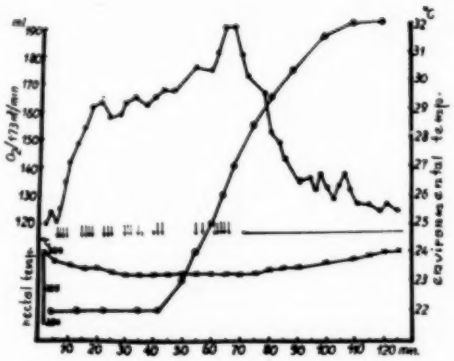

Fig. 2. Full-term infant. Age, 7 days; weight, 2,800 grams (6 pounds, 3 ounces). ●——● = O_2 consumption; ×——× = rectal temperature; ○——○ = environmental temperature; ↓↓ = restlessness; —— = asleep.

ingly restless, and O_2 consumption increased approximately 100 per cent. At the same time the rectal temperature decreased at a relatively constant rate. O_2 consumption in the more usual environment of 30° to 33° C. (86° to 91.4° F.) was identical with that observed at the beginning of the experiment in the colder environment when the infant was asleep.

Fig. 5 shows another experiment on the same premature infant at the age of 8 days. Basal metabolism on the basis of body surface was already considerably higher, but still less than that of an infant at several months of age. The increase in O_2 consumption in the cool environment was less on the eighth day than on the first and, in spite of this, the body temperature was maintained throughout the experiment. This observation suggests that even in the premature infant the inclination to hypothermia in the first days of life cannot be explained solely by the lesser increase in the production of heat. Since O_2 consumption of the quietly sleeping infant is identical at 20° C. and at 30° to 32° C., proof for the activity of chemical thermoregulation, in the strictist sense, was not obtained.

In Fig. 6 the O_2 consumption of a sleeping premature infant 4 days of age is seen to be quite constant at a temperature of 32° C. (89.6° F.). Cooling of the environment elicited intensive restlessness accompanied by a marked increase in heat production. The fluctuations of O_2 consumption followed closely the changing intensity of muscular activity. When the infant fell asleep, O_2 consumption returned to the basal level.

DISCUSSION

The results reported here show clearly that below the usual environmental tem-

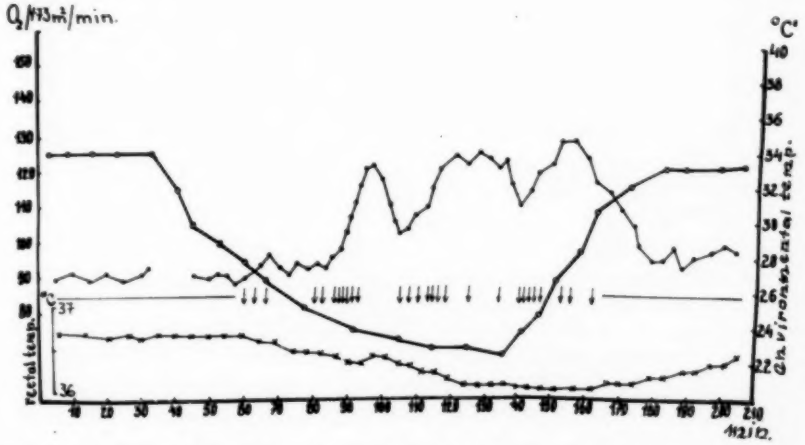

Fig. 3. Full-term infant. Age, 3 days; weight, 2,900 grams (6 pounds, 5 ounces). ●——● = O_2 consumption; ×——× = rectal temperature; ○——○ = environmental temperature; ↓↓ = restlessness; —— = asleep.

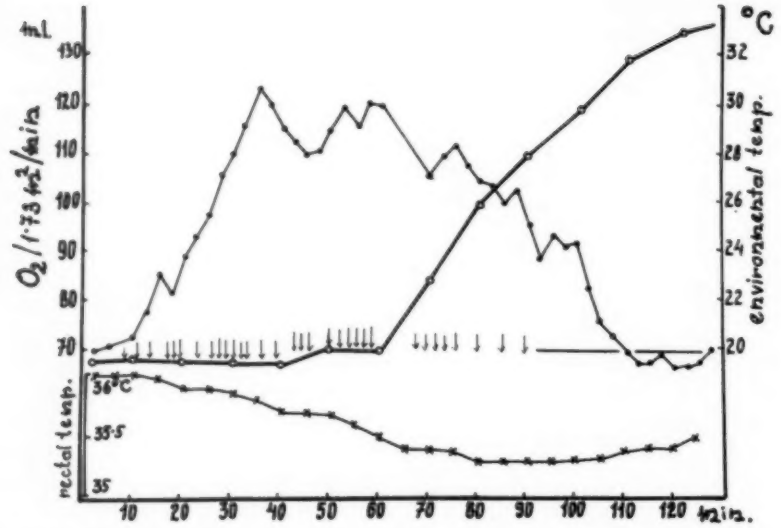

Fig. 4. Premature infant. Age, 1 day; weight, 1,890 grams (4 pounds, 3 ounces). ●——● = O_2 consumption; ×——× = rectal temperature; ○——○ = environmental temperature; ↓↓ = restlessness; —— = asleep.

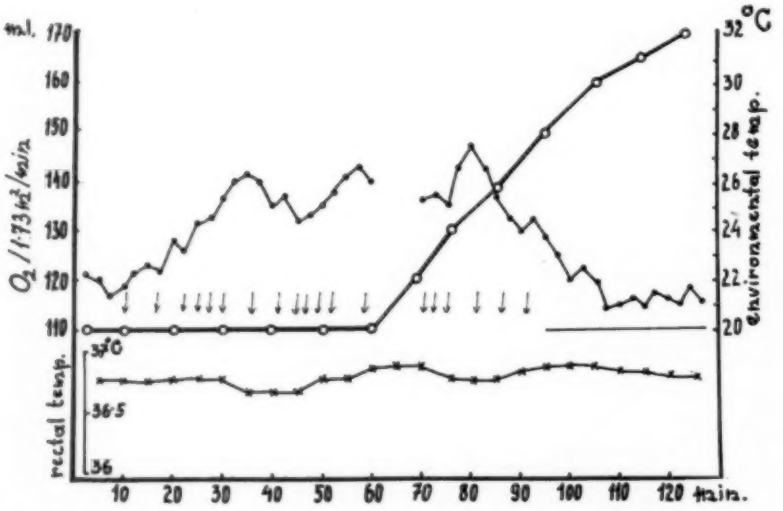

Fig. 5. Premature infant. Age, 8 days; weight, 2,000 grams (4 pounds, 7 ounces). ●——● = O_2 consumption; ×——× = rectal temperature; ○——○ = environmental temperature; ↓↓ = restlessness; —— = asleep.

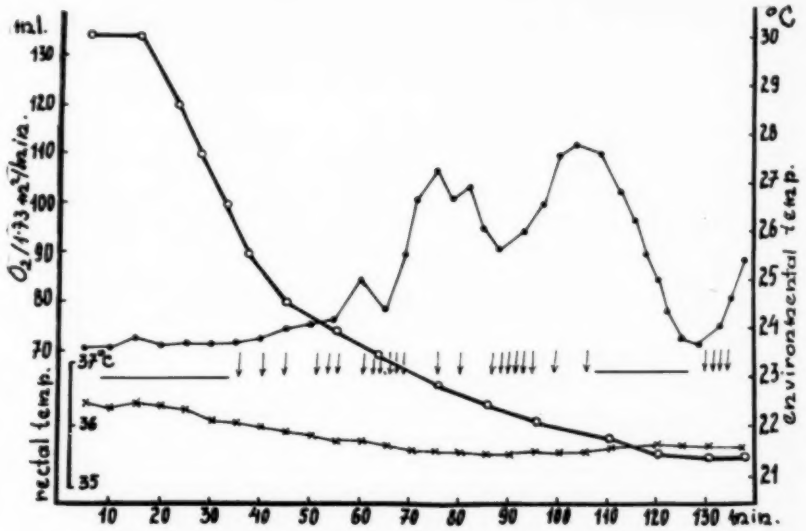

Fig. 6. Premature infant. Age, 4 days; weight, 1,760 grams (3 pounds, 14 ounces). ●——● = O_2 consumption; ×——× = rectal temperature; ○——○ = environmental temperature; ↓↓ = restlessness; —— = asleep.

perature of 30° to 33° C. (86° to 91.4° F.) in which newborn infants are maintained, the production of heat increases strikingly in both full-term and premature infants. This increase is always associated with more or less intensive muscular activity. The marked regulatory reaction of heat production in the premature infant is particularly interesting in relation to the demonstration by Kerpel-Fronius, Varga, and Kun[12] of the inadequacy of chemical thermoregulation in severely malnourished infants. Our observations leave no doubt that muscular activity plays an important role in the defense against cooling in the neonatal period. The role of muscular activity in chemical thermoregulation of full-term and premature infants is very conspicuous—the half-naked sleeping infant is aroused in a few minutes by an environment of 20° to 22° C. (68° to 71.6° F.) and becomes restless. Muscular activity is at first intermittent. Sleeping and waking periods alternate with individually varying frequencies; O_2 consumption accordingly often shows marked fluctuations. Rectal temperatures of full-term infants at 1 to 5 days of age fall gradually, but at 6 to 10 days of age the infants maintain their body temperature. Restlessness increases with the time of exposure; now and then transient shivering can be observed, yet during rest O_2 consumption falls to the basal level. Ultimately, a stage of very intensive and uninterrupted restlessness is reached, and during this the infant can be calmed only by elevation of the environmental temperature.

Since our observations were usually begun in a cool environment, it may be that the close correlation between increased activity and cool environment is more apparent than real. Restlessness could have been due to the experimental procedure and might have ultimately subsided without the elevation of environmental temperature. The same correlation was found, however, in experiments in which the infants were observed initially for the same period of time at an environmental temperature of 29° to 30° C. (84.2° to 86° F.).

It would seem that in the neonatal period shivering is not an important factor in chemical thermoregulation. The fact that muscular activity enables the infant to increase the production of heat considerably, as well as the observations of Brück[13-15] that neonates possess an effective physical thermoregulation, indicates that thermoregulation of the infant does not differ essentially from that of the adult. This does not mean, however, that an environment much cooler than room temperature is as well tolerated by the newborn infant as by the adult. In spite of physical and chemical thermoregulation, the defense against cooling in the first day of life is inadequate—exposure of the infant, when half naked, to an average room temperature is followed by a variable decrease in body temperature. According to Brück,[10] this decrease is due exclusively to the infant's limited ability to increase the production of heat. The observation that body temperature may fall in some instances at a constant rate in spite of the marked and lasting increase in the production of heat, whereas in others the body temperature may be maintained with a lesser increase in the production of heat, does not support this assumption. We believe that in the full-term newborn infant the initial fall and the subsequent stabilization of the body temperature at a low level are not due simply to an inadequate production of heat, but rather that they represent a change in the central regulation of body temperature. This assumption is supported by the observation that in an infant at 8 to 10 days of age, the increase in the production of heat may not be marked, but, in spite of this, the body temperature may be maintained at the initial level.

The unfavorable surface-volume relationship and the greater or lesser insufficiency of physical thermoregulation tend to be most important in the smallest premature infants and, in these, even a considerable increase in the production of heat could be insufficient to maintain body temperature; the increase of blood flow in the musculature could possibly even enhance heat loss.[15] A similar assumption, however, could hardly explain the fact that an infant at 6 to 10 days of age maintains body temperature in a cool environment with a smaller increase in the production of heat when an infant at 1 to 6 days of age, in the same environment, has a fall in body temperature.

Although muscular activity and an increase in the production of heat were closely linked in our observations, the possibility of an increase in the production of heat in other tissues, e.g., the liver and intestines cannot be excluded, since, at least in the rat, the thermoregulatory increase of the production of heat may precede the onset of muscular activity under comparable experimental conditions.[16]

SUMMARY

Chemical thermoregulation of full-term and premature newborn infants from 1 to 10 days of age was investigated by the continuous recording of O_2 consumption and rectal temperatures. The results show clearly that, in an environment cooler than the usual nursery or incubator temperature, the striking increase in O_2 consumption is always associated with more or less intense muscular activity. During rest in the same environment O_2 consumption falls to the basal level. Although there is a close parallelism between the production of heat and muscular activity, the possibility of increased thermogenesis in other organs cannot be excluded. In spite of chemical thermoregulation the defense against cooling in the first days of life is inadequate. According to our opinion, the initial fall and subsequent stabilization of body temperature at a lower level in the full-term infant is not due simply to inadequate production of heat but represents a change in the centrally regulated control of body temperature.

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Comparison of arterial and arterialized blood in normal newborn infants and older children with congenital heart lesions

M. A. Mullinger, M.D.,* J. A. Niblock, B.A., and M. D. Young, M.B., M.R.C.P.

VANCOUVER, BRITISH COLUMBIA

THE DETERMINATIONS of arterial oxygen and carbon dioxide contents and of per cent oxygen saturation are procedures of value in the diagnosis of congenital heart lesions. It is often difficult and hazardous to obtain arterial blood samples from infants, however.

Lilienthal and Riley,[1, 2] Lundsgaard and Moller,[3] and Hultgren and Hackett[4] have shown that the pH, oxygen content, oxygen saturation, and carbon dioxide content of capillary blood of tissues through which arterial blood has been flowing rapidly approach the values of arterial blood itself. Such rapid flow may be produced by applying heat to the part or injecting histamine. Comparison of values for oxygen and carbon dioxide content of arterial and of capillary blood arterialized by these methods in the same patient has been reported only in normal adults. Should this alteration in capillary blood flow in infants and young children be comparable to that in adults, then the oxygen content, oxygen saturation, and carbon dioxide content determinations could be made on capillary blood from a heel puncture after warming of the extremity.

This report describes microgasometric whole blood analyses and the determination of hemoglobin content of arterial and "arterialized" capillary blood in normal newborn infants and in older children with congenital heart lesions.

From the Health Centre for Children, Department of Paediatrics, The University of British Columbia.

**Address, Faculty of Medicine, Department of Paediatrics, The University of British Columbia, 715 West 12th Avenue, Vancouver 9, B. C., Canada.*

METHODS AND MATERIALS

To evaluate the so-called arterialization of capillary blood in newborn infants, a series of 22 normal, full-term infants born by the vaginal route, by outlet forceps, or by normal spontaneous delivery following various forms of maternal anesthesia were studied during their stay in the nursery. One infant was studied on two separate occasions. Age at sampling varied from 1 hour to 10 days. Arterial samples were obtained from the temporal or femoral artery. Simultaneously, "arterialized" capillary blood samples were obtained from the heated heel as described below. Comparison of the results for oxygen, carbon dioxide, and hemoglobin contents of the two samples from each baby was made.

Concurrently, a similar study was made of 22 children with congenital heart defects who varied in age from 10 months to 17 years. One child was studied on two occasions. This group included both cyanotic and noncyanotic patients. The arterial blood was obtained from the femoral artery or radial artery, and the "arterialized" capillary blood was obtained from the heated heel in the same manner as in the normal infants.

In drawing arterial blood, the plunger of a syringe was coated thinly with mineral oil and a short-beveled No. 22 needle was sealed on to the syringe with collodion. About 0.1 c.c. of liquid heparin (1,000 units per cubic centimeter) was drawn into the syringe to wet the inside of the barrel. Any air bubbles present then were expelled with the excess heparin, leaving only the dead space of the syringe and the needle filled with heparin. "Arterialized" capillary blood (hereafter referred to as capillary blood) was obtained by heating the infant's or child's foot for 5 minutes in a water bath at 45° C., puncturing the lateral margin of the heel with a sharp No. 11 Bard-Parker blade, and allowing the freely flowing blood to drop through neutral mineral oil into a glass collecting apparatus (Fig. 1). Dried heparin was used as the anticoagulant and a drop of mercury was placed at the bottom of the collecting tube to aid in mixing. All samples were placed in ice as soon as they were taken and maintained in ice until all analyses were completed.

On 37 of the samples of blood, microdeterminations of oxygen and carbon dioxide levels were standardized against the manometric method of Van Slyke and Neill.[6] Satisfactory agreement between the duplicate analyses by each method was obtained (Table I). Measurement of oxygen and carbon dioxide content was made on every blood sample by the micro method described by Scholander, Flemister, and Irving.[5] Hemoglobin concentration was determined with the Klett-Summerson photocolorimeter with the use of ammonium hydroxide solution.[7] Analyses of all samples were performed in duplicate.

RESULTS

The results of analysis of the oxygen, carbon dioxide, and hemoglobin contents of arterial and capillary blood in 22 normal newborn infants are summarized in Table II. In them the average oxygen levels were 20.8 ± 2.08 volumes per cent in the capillary blood and 20.7 ± 2.76 volumes per cent in the arterial blood. The average carbon dioxide content of the capillary blood was 34.9 ± 4.0 volumes per cent and of the arterial blood was 36.4 ± 5.3 volumes per cent. The average capillary hemoglobin was 17.6 ± 1.73 Gm. per cent and the arterial blood hemoglobin was 17.7 ± 1.85 Gm. per cent.

In 3 of the newborn infants the oxygen content of the capillary blood was 3 volumes per cent higher than in the arterial blood, while in one infant it was 4 volumes per cent lower than in the arterial blood.

In 4 infants the carbon dioxide content of capillary blood was 6 volumes per cent less and in 1 it was almost 10 volumes per cent higher than in the arterial blood.

Fig. 1.

Table I. Analysis of duplicate tests (37 pairs of duplicates in all tests)

Method	*Test*	*Mean difference*	*Standard deviation of mean*	*Standard error of mean*
Van Slyke	Oxygen	0.3	0.2	0.02
Scholander	Oxygen	0.4	0.7	0.10
Van Slyke	Carbon dioxide	0.5	0.1	0.16
Scholander	Carbon dioxide	0.7	0.1	0.01

Table II. Analysis of arterial and arterialized capillary blood of newborn infants

Name	*Age*	*Oxygen (vol. %)*		*Carbon dioxide (vol. %)*		*Hemoglobin (Gm.)*		*Crying*
		Arterial	*Capillary*	*Arterial*	*Capillary*	*Arterial*	*Capillary*	
And	19 hours	17.4	21.2	38.7	33.2	17.1	18.0	-
Mun	17 hours	20.9	19.4	42.3	33.5	—	15.0	-
Kel	6 days	24.2	22.7	32.3	33.3	18.0	18.5	-
Mun	10 days	20.9	18.6	41.1	24.8	19.5	14.8	-
Ser	27 hours	16.1	18.1	46.2	43.6	15.1	14.6	-
Rob	17 hours	21.4	21.1	37.6	38.3	17.5	18.1	-
Keh	13 hours	24.8	24.6	37.6	34.9	18.7	20.0	-
Bee	8 hours	21.4	22.0	36.1	39.0	17.4	18.5	-
Col	8 days	17.2	18.9	43.9	38.5	15.0	15.1	-
McL	7 hours	24.4	22.3	33.2	33.7	19.8	18.9	-
Wil	38 hours	24.9	23.4	24.4	34.3	19.4	18.7	-
Owe	5 days	19.6	19.2	30.2	29.5	14.9	15.8	-
Nad	16 hours	22.9	21.7	33.6	38.3	17.7	17.9	-
Mar	2½ days	17.2	17.8	29.7	31.6	19.1	19.4	C
Urb	12 hours	23.9	23.6	32.5	32.3	18.3	20.1	-
Kob	19 hours	20.0	20.3	37.4	37.8	15.6	16.7	-
Hig	11 hours	21.4	24.5	33.5	36.9	18.2	19.9	-
Lar	14 hours	15.2	19.8	39.3	36.9	15.4	16.7	-
Kro	1 hour	21.0	21.0	29.9	34.3	16.4	16.2	-
Hyn	43 hours	21.6	21.4	41.2	29.3	22.3	18.7	C
McD	2 days	20.3	24.2	42.4	35.6	18.3	18.8	C
Tho	14 hours	21.2	22.1	37.4	35.3	20.3	18.6	C
Rul	16 hours	19.6	20.6	38.6	39.7	16.4	16.8	-
Average		20.7	20.8	36.4	34.9	17.7	17.6	
Standard deviation		2.76	2.08	5.3	4.0	1.85	1.73	
Standard error		0.56	0.43	1.1	0.84	0.38	0.36	

The values for oxygen, carbon dioxide, and hemoglobin in arterial and capillary blood in the 22 older children with congenital heart lesions are summarized in Table III. In this group it is seen that the average oxygen content of the capillary blood was 14.8 ± 3.0 volumes per cent while the arterial blood was 14.5 ± 3.6 volumes per cent. The average carbon dioxide content of the capillary blood was 13.8 ± 2.1 Gm. per cent and of the arterial blood was 12.8 ± 1.5 Gm. per cent.

DISCUSSION

When comparison of arterial and capillary heel blood was made in 22 normal newborn infants ranging in age from 1 hour to 10 days, age did not appear to influence the difference between the arterial and capillary levels of oxygen, carbon dioxide, or hemoglobin in the same infant (Table II).

Most infants did not cry when the heel was pricked but some cried when an arterial sample was taken. Those who cried forcibly are noted in Table II. There is an occasional

Table III. Analysis of arterial and arterialized capillary blood in older children with congenital heart lesions

Name	Age	Oxygen (vol. %)		Carbon dioxide (vol. %)		Hemoglobin (Gm.)		Crying	Cyanotic
		Arterial	Capillary	Arterial	Capillary	Arterial	Capillary		
Del	3 years	0.6	3.7	30.1	28.7	16.4	18.6	–	+++
Lud	26 months	12.1	13.5	38.1	36.9	12.5	12.4	–	0
Rog	4 years	19.9	19.4	32.2	31.8	—	(26.4)	–	+++
L. Smi	6 years	15.4	15.9	41.2	38.7	13.5	13.8	–	0
Cha	18 months	14.6	14.8	31.3	32.0	11.9	12.6	–	0
Ric	9 years	14.0	14.6	44.2	46.0	12.4	12.8	–	0
Ree	17 years	18.0	17.7	42.4	43.8	14.5	15.4	–	0
Lou	10 years	16.3	16.5	37.5	38.1	14.0	14.4	–	+
Dut	5½ years	15.3	15.1	35.6	39.7	13.7	13.7	–	+
Bat	7½ years	14.0	13.0	41.1	43.2	11.2	10.5	C	0
Pat	8 years	16.3	17.3	37.9	38.9	—	(14.4)	–	+
Wilk	2 years	15.0	18.1	44.2	43.2	—	(14.9)	–	0
Tso	2 years	15.1	15.5	41.0	42.8	—	(15.2)	–	+
Feh	5½ years	13.4	13.2	42.6	44.6	12.2	11.0	–	0
Rie	1 year	14.4	14.2	36.6	34.4	13.9	12.1	C	0
Caw	6 years	17.0	16.5	50.1	44.9	12.7	12.7	–	+
Stu	10 months	13.2	12.3	51.9	43.3	11.0	10.1	–	0
G. Smi	6½ years	15.3	15.0	42.9	39.8	12.4	12.3	–	0
Stu	10 months	11.9	12.2	37.4	36.6	10.0	10.7	–	0
Nis	12 years	17.7	15.6	41.0	43.6	13.7	13.8	–	0
Will	7 years	16.3	15.3	42.8	40.7	14.2	15.0	C	0
Sin	8 years	17.1	15.6	44.0	39.9	13.6	13.9	C	0
Hob	7 years	11.8	15.0	45.1	45.9	10.6	11.6	–	0
Average		14.5	14.8	40.4	39.8	12.8	13.8		
Standard deviation		±3.6	±3.0	±5.4	±4.8	±1.5	±2.1		
Standard error		0.75	0.62	1.1	1.0	0.28	0.39		

lack of correlation between the arterial and capillary values of oxygen content and more frequently of carbon dioxide of some of the infants, and it is suggested that this variation may be accounted for by the effects of crying and of holding the breath. There is an insufficient number of children known to be crying or to be holding their breath at the time of sampling to make analysis of results under such circumstances statistically significant.

There is good correlation between the oxygen content as measured in the arterial and capillary blood in almost all the older children with congenital heart lesions. Only 4 differed by 2 volumes per cent or more. The correlation between the arterial and capillary values for carbon dioxide content is better in this group of children than in the newborn infants. Only 3 of these children cried when the blood samples were collected, and apparently this crying was not sufficient to affect the carbon dioxide content or oxygen content of the blood. Age did not appear to influence the difference between arterial and capillary levels of oxygen, carbon dioxide, or hemoglobin in the same child, as noted in Table III. The presence or absence of cyanosis did not appear to result in a difference in oxygen, carbon dioxide, or hemoglobin contents in the arterial and capillary bloods in any patient.

Eldridge and his co-workers[8] occasionally noted in newborn infants differential cyanosis of the lower part of the body as compared to the upper part, similar to that observed in patients with a patent ductus arteriosus with reversed flow. In each of 12 newborn infants, they studied the arterial oxygen saturation of capillary blood in the upper and lower extremities at varying times after birth. On the basis of their observations they

suggested that there might be a reverse ductus flow in some of these patients. They made no note regarding which infant showed clinical differential cyanosis of the extremities. The possibility of local immaturity in the peripheral circulation of the lower extremities was not considered.

In our studies of newborn infants, 15 arterial samples were obtained from the temporal artery and 8 arterial samples were obtained from the femoral artery. Determinations of oxygen, carbon dioxide, and hemoglobin contents in these were compared with those of arterialized capillary heel blood from the same patient. There was essentially little difference in the two groups, i.e., variation in differences in the contents of oxygen, carbon dioxide, and hemoglobin were similar in the two groups, irrespective of age at the time of sampling.

SUMMARY

1. A comparison of arterial and "arterialized" capillary blood was made in each of 22 normal full-term infants varying in age from 1 hour to 10 days at the time of sampling. The average blood oxygen level in the capillary blood was 20.8 ± 2.08 volumes per cent and in the arterial blood 20.7 ± 2.76 volumes per cent. The average carbon dioxide content of the capillary blood was 34.9 ± 4.0 volumes per cent and in the arterial blood 36.4 ± 5.3 volumes per cent. The average hemoglobin content of the capillary blood was 17.6 ± 1.73 Gm. per cent and in the arterial blood 17.7 ± 1.85 Gm. per cent. Age at sampling did not appear to influence the difference between the arterial and capillary levels of oxygen, carbon dioxide, or hemoglobin in the same infant. It is considered that when the oxygen content is to be measured in the newborn infant, "arterialized" capillary blood may be used if arterial blood is difficult to obtain. It is of less value when the carbon dioxide content is to be measured in newborn infants.

2. A comparison of arterial and "arterialized" capillary blood was made in each of 22 older children with congenital heart lesions. The oxygen content of the capillary blood averaged 14.8 ± 3.0 volumes per cent and of the arterial blood 14.5 ± 3.6 volumes per cent. The average carbon dioxide content of the capillary blood was 39.8 ± 4.8 volumes per cent and of the arterial blood 40.4 ± 5.4 volumes per cent. The average hemoglobin content of the capillary blood was 13.8 ± 2.1 Gm. per cent and of the arterial blood 12.8 ± 1.5 Gm. per cent. Neither age at the time of sampling nor degree of cyanosis seemed to affect appreciably the levels of gas or hemoglobin in these samples.

It is considered that arterialized capillary blood may be used when arterial blood is difficult to obtain.

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Interrelationships in the urinary excretion of creatine, creatinine, free alpha amino acid nitrogen, and total nitrogen in premature infants

Jens Bergstedt, M.D.,* Donough O'Brien, M.D., M.R.C.P., and Lula O. Lubchenco, M.D.**

DENVER, COLO.

AS LONG as 50 years ago it was claimed[1, 2] that the 24-hour excretion of creatinine was constant for the adult individual. More recently a highly significant ratio apparently was shown between body weight and daily excretion of creatinine in infants.[3] As a result of this work, it was suggested that urinary creatinine might be used as a check on the probable validity of a 24-hour sample.[4] A number of other studies, however, have suggested rather wide ranges in the urinary creatinine excretion coefficient (milligrams per kilogram per 24 hours) in infants, children, and adults,[5, 6, 7, 9] with coefficients of variation ranging from 7.8 per cent to 19.6 per cent.[8, 10, 11] For these reasons there seemed to be little justification for the practice of expressing other urinary solutes, such as amino acids, in terms of their ratios to creatinine and thus comparing the excretion in a group of individuals on untimed samples.[12, 13, 14]

The objective of this study was to investigate these apparently conflicting claims by establishing the interrelationship and degree of constancy of excretion of various components of urinary nitrogen in a group of premature infants, both in single voidings and in 24-hour samples.

MATERIAL AND METHODS

Ten healthy premature infants who weighed 1,100 to 2,110 grams and who ranged in age from 2 to 12 weeks were placed on a metabolic frame; each voiding was collected for one or two 48- or 72-hour periods in a time-flow fraction collector. The

From the Department of Pediatrics, University of Colorado, Denver, Colo.

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**Present address: Pediatric Clinic, Kronprintessan Lovisas Barnsjukhus, Stockholm, Sweden.*

***John and Mary Markle Foundation Scholar in Medical Sciences. Address, Department of Pediatrics, University of Colorado Medical Center, 4200 East Ninth Avenue, Denver 20, Colo.*

Table I. The excretion coefficients* of the components of total urinary nitrogen

	Mean	*Range*		*Coefficient of variation†*		*No. of observations*	
	Single voidings	*Single specimens*	*24-hour sample*	*Single specimen (%)*	*24-hour sample (%)*	*Voidings*	*24-hour samples*
Creatinine	14.3	2.5 to 101.6	8.3 to 19.9	74	23	436	34
Creatine	2.3	0.03 to 11.4	0.3 to 4.3	100	43	206	17
Total nitrogen	239	23 to 819	119 to 270	56	24	206	17
Amino acid nitrogen	20.7	2.7 to 74.5	10.0 to 26.8	69	28	206	17

*Excretion coefficient $= \frac{\text{milligrams in sample} \times 24 \div \text{collection time in hours}}{\text{weight of subject in kilograms}}$.

†Coefficient of variation $= \frac{\text{standard deviation}}{\text{mean}} \times 100$.

Table II. Relationship of individual nitrogen components to total nitrogen in single and 24-hour voidings

	Mean total nitrogen (%)	*Range total nitrogen (%)*		*Coefficient of variation**		*No. of observations*	
	Single voidings	*Single specimen*	*24-hour sample*	*Single specimen (%)*	*24-hour sample (%)*	*Voidings*	*24-hour samples*
Creatine nitrogen	0.35	0.02 to 1.5	0.1 to 1.0	100	69	206	17
Creatinine nitrogen	2.0	0.7 to 4.3	1.2 to 2.7	25	14	206	17
Amino acid nitrogen	9.2	3.0 to 23.3	5.0 to 11.2	30	8	206	17

*Coefficient of variation $= \frac{\text{standard deviation}}{\text{mean}} \times 100$.

individual urine voidings were removed several times a day, preserved by the addition of a thymol crystal, and stored in a freezer until separately analyzed. The urinary creatine and preformed creatinine were determined by the Jaffé reaction after ether extraction of interfering chromogens[15]; free alpha amino nitrogen was measured by the copper method,[16] and the total urinary nitrogen by a standard micro-Kjeldahl method with the use of selenium as a catalyst. The infants were fed a conventional evaporated milk formula containing 530 to 770 mg. of nitrogen per kilogram per 24 hours (mean, 700 mg. per kilogram per 24 hours) in total volumes ranging between 130 ml. and 180 ml. per kilogram per 24 hours (mean, 163 ml. per kilogram per 24 hours).

RESULTS AND DISCUSSION

Collections were made for 34 24-hour periods and included 436 individual voidings. The latter had a mean volume of 5.4 ml. per kilogram (1.3 to 17.5 ml.), representing a mean urinary flow of 3.8 ml. per kilogram per hour (0.4 to 22.8 ml.). The frequency of voiding averaged 12.8 times per 24-hour period (range 8 to 19), with an average interval between voidings of 1.9 hours (30 minutes to 5½ hours).

Table I shows the excretion coefficients (milligrams per kilogram per 24 hours) of the urinary nitrogen constituents and also the considerable range in the rate of excretion of these fractions both for single voidings and for 24-hour samples. The figures not only demonstrate the inherent variability of the excretion of creatinine in terms of body weight but show that the range in the excretion of the other urinary nitrogen components transcended that which might have been anticipated from differences in intake or, in the case of amino acids, from stoichiometric variation in assay. Moreover,

this variability also, at least in respect to 24-hour pools, seems unlikely to have been accounted for by incomplete emptying of the bladder in view of the over-all frequency of voiding. The rather high values for free alpha amino nitrogen are considered to be a reflection of the use of the copper method without previous extraction by an ion exchange column.[17] The values for creatine, creatinine, and total nitrogen are comparable, however, to those of earlier studies.[7, 12]

Table II shows further that in both single voidings and in 24-hour pools neither creatinine nitrogen nor creatine nitrogen was excreted in an amount which was a constant proportion of the total nitrogen excreted. The only significantly constant relationship in the urine was between free amino acid nitrogen and total nitrogen in the 24-hour samples.

Tables III and IV show similarly wide ranges for the amino acid nitrogen to creatinine nitrogen and for the creatine to creatinine ratios.

Table III. Amino acid nitrogen: creatinine-nitrogen ratio

	Mean	*Range*	*Coefficient of variation (%)*	*No. of observations*
Single voidings	4.6	0.85 to 10.30	38	206
24-hour specimens	4.6	1.85 to 7.36	32	17

Table IV. Creatine as a fraction of total creatinine in 24-hour samples

Mean (%)	*Range (%)*	*Coefficient of variation (%)*	*No. of observations*
14	2 to 25	44	17

These data indicate that there is great variance in the excretion of the components of urinary nitrogen, not only absolutely but in relation to each other and not only be-

Table V. Range in the excretion coefficients* of the urinary nitrogen components in 6 infants in serial voidings over a single 24-hour period and in 3 consecutive 24-hour pools

Infant	*Total nitrogen*			*Free alpha amino acid nitrogen*			*Creatine*			*Creatinine*		
	Mean	*Range*	*C.V. (%)†*	*Mean*	*Range*	*C.V. (%)†*	*Mean*	*Range*	*C.V. (%)†*	*Mean*	*Range*	*C.V. (%)†*
All voidings in one 24-hour period												
Du	190	83 to 503	57	12	3.8 to 29.5	29	2.0	0.1 to 4.9	55	11.2	4.6 to 32.6	72
Sm	307	92 to 743	31	22	8.7 to 56.9	62	3.3	0.5 to 10.5	91	16.0	3.6 to 43.2	69
Th	188	145 to 317	57	21	12.7 to 39.5	70	1.7	0.7 to 3.0	71	10.7	8.8 to 17.3	52
Gr	211	103 to 354	58	20	6.1 to 45.4	67	1.6	0.5 to 3.3	74	12.7	4.6 to 34.6	62
Br	168	108 to 335	76	10	7.0 to 27.0	87	0.5	0.1 to 1.2	88	10.7	5.5 to 21.8	56
Au	300	30 to 819	66	26.8	6.9 to 74.5	70	3.1	0.3 to 11.4	78	18.6	4.3 to 58.1	44
	Mean	*Range*		*Mean*	*Range*		*Mean*	*Range*		*Mean*	*Range*	
3 consecutive 24-hour pools												
Du	159	119 to 191		13.3	10.3 to 16.1		1.9	1.6 to 2.6		11.4	10.7 to 12.6	
Sm	222	175 to 270		20.3	19.3 to 22.2		2.8	1.6 to 3.6		13.8	13.4 to 14.1	
Th	191	188 to 199		20.7	19.2 to 21.9		1.2	0.9 to 1.7		9.5	8.6 to 10.1	
Gr	242	203 to 270		15.6	12.5 to 24.3		1.9	1.1 to 3.2		14.7	11.5 to 19.9	
Br	169	163 to 173		12.9	10.0 to 15.9		1.0	0.3 to 1.8		11.3	10.7 to 12.1	
Au	177	154 to 200		22.0	17.3 to 26.8		3.7	3.1 to 4.3		15.8	13.0 to 18.6	

*Excretion coefficient $= \frac{\text{milligrams in sample} \times 24 \div \text{collection time in hours}}{\text{weight of subject in kilograms}}$.

†C.V. = Coefficient of variation $= \frac{\text{standard deviation}}{\text{mean}} \times 100$.

tween infants, but between serial voidings and 24-hour collections in the same infant (Table V). Certainly it shows that, in the premature infant, comparisons of any given urinary solute, such as amino acids, based on the creatinine ratio in single voidings, would be liable to considerable errors in interpretation.

SUMMARY

1. The urinary excretion in milligrams per kilogram per 24 hours for creatine, creatinine, free alpha amino acid nitrogen, and total nitrogen have been recorded for a group of premature infants 2 to 12 weeks of age in both single voidings and in 24-hour pools.

2. A considerable range was noted in the excretion coefficients (milligrams per kilogram per 24 hours) of all the components of urinary nitrogen investigated, not only between different infants but between single voidings and 24-hour pools of the same infant. The only significantly constant interrelationship was between free alpha amino nitrogen and total nitrogen in the 24-hour samples.

3. The practice of expressing the urinary excretion of a substance of premature infants in terms of the creatinine ratio is likely to lead to erroneous conclusions, particularly where this is done on single voidings.

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Transient granulocytopenia of the newborn associated with sepsis due to Shigella alkalescens and maternal leukocyte agglutinins

A case report

Joseph P. Rossi, M.D.,* and Ira K. Brandt, M.D.

NEW HAVEN, CONN.

IN 1950 Slobody and his associates[1] reported a case of agranulocytosis in a newborn infant 75 hours old. Despite negative blood cultures, they concluded that the etiological factor was probably sepsis because of fever, irritability, and poor feeding. Lehndorff,[2] in 1951, described the same infant and his younger sibling who also developed transient, severe granulocytopenia on the third day of life, without demonstrable sepsis. He termed this condition "transient granulocytopenia of the newborn." In 1956, Luhby and Slobody[3] presented the same siblings and suggested that leukocyte agglutinins might have been responsible for the granulocytopenia, however, they were apparently unable to demonstrate their presence. Schümer[4] in 1953, reported upon a 7-day-old infant with agranulocytosis, omphalitis, and pyoderma. Antibiotics were administered and steady improvement occurred with return of the white blood count to normal at 3 weeks of age. In 1959, Lalezari and co-workers[5] described a family in which several siblings developed neutropenia in the newborn period. The mother possessed potent leukoagglutinins against her children's and husband's cells, and it was felt that the neutropenia had been brought about in a manner analogous to the anemia of hemolytic disease of the newborn.

In the present case, severe granulocytopenia was discovered at the age of 3 days; this progressed to complete absence of the circulating neutrophils on the sixth day of life, with remission taking place during the subsequent 10 days. At the onset, a gram-negative enteric microorganism, *Shigella alkalescens,* was isolated in pure culture from the infant's nose, throat, and blood. Review of the literature did not reveal any cases either of sepsis of the newborn due to *Shigella alkalescens,* or of severe neutropenia associated with infection due to this microorganism. Some months after the episode of neutro-

From The Department of Pediatrics, Yale University School of Medicine.

**Address: Department of Pediatrics, Yale University School of Medicine, 333 Cedar Street, New Haven 11, Conn.*

penia, the serum of the patient's mother was demonstrated to possess antibody against the neutrophils of both the infant and the father.

CASE REPORT

Clinical course. The patient was a white male infant, the product of a normal, full-term, spontaneous delivery, who weighed 3,940 grams at birth. The mother was a primigravida and her pregnancy had been uneventful. Her serologic test for syphilis was negative, and she had no allergy or chronic disease. Total labor lasted 10 hours and 52 minutes. At birth the infant breathed and cried spontaneously.

Physical examination shortly after birth showed the infant to have a good color and a lusty cry and was otherwise unremarkable. Splenomegaly, petechiae, and lymphadenopathy were not present. Feedings of an evaporated milk formula were started at 12 hours of age.

At 24 hours of age a shrill cry and arching of the back were noted. Shortly thereafter, following a feeding, recurrent clonic movements of the left hand at the rate of 1 per second were seen; these lasted for approximately 5 minutes. At this time the physical examination was otherwise negative. A similar episode occurred later in the evening.

At the age of 48 hours the infant was examined because of a sudden increase in the respiratory rate following an uneventful feeding. Respirations were 120 per minute and were shallow and irregular; his color, however, remained good. Occasional episodes of rapid twitching of the eyelids were seen, each lasting approximately 5 seconds. When aroused during examination he uttered a shrill cry and assumed the opisthotonic position. These signs persisted but the seizures never recurred.

At about 72 hours of age the infant developed intermittent cyanosis. His color appeared normal, his weight was 3,800 grams, and he was fairly active. Marked intermittent tachypnea with occasional periods of shallow, irregular breathing, was noted. No icterus could be seen. The spleen was palpable 2 cm. below the left costal margin and was soft. The liver edge was 1 cm. below the right costal margin. The umbilical stump was clean and dry. There was a high-pitched, hoarse cry. The sucking reflex was vigorous, and the Moro reflex was brisk and symmetrical. The extremities appeared hypertonic, but there was no asymmetry of tonus. The grasp reflex was strong and equal bilaterally. The body temperature was normal and the remainder of the examination was negative.

At this time the infant's formula was supplemented with 2 Gm. of calcium gluconate; this was discontinued 24 hours later when a serum calcium of 8.3 mg. per 100 ml. was reported. After blood was obtained for culture, intramuscular administration of penicillin (200,000 units) and chloramphenicol (200 mg.) at 12-hour intervals was begun as a prophylactic measure.

The infant's spleen gradually enlarged over a 3-day period to 3.5 cm. below the left costal margin and became very firm. He continued to feed well and gradually began to gain weight. Antibiotics were discontinued after 13 days of treatment. At 20 days of age the patient was discharged in good condition.

At 29 days of age the infant was seen again. His weight was 4,500 grams and he appeared to be thriving. The spleen was palpable 1.5 cm. below the left costal margin and was soft. The white blood count and bone marrow aspirate were normal. Blood, stool, and urine cultures, and serum agglutination tests, using the organisms grown from the patient's blood, were performed on the mother at this time but did not indicate infection with *Shigella alkalescens.* Thereafter the infant was seen at intervals of 2 or 3 weeks. He contined to do well, and at 78 days of age, the spleen was no longer palpable. At the time of his last visit at 15 months of age he appeared in excellent condition. Physical examination was negative, and the hemogram was normal. Developmental examination revealed a performance adequate for his chronological age.

Laboratory results. Serial blood counts are given in Table I and Fig. 1. It will be

seen that leukopenia and granulocytopenia were present on the third day of life and that by the sixth day of life the neutrophils had completely disappeared from the peripheral blood. There was an absolute increase in monocytes which reached a peak on the eleventh day of life at which time neutrophils first reappeared. As the number of neutrophils increased there was a concurrent fall in monocytes until, by the sixteenth day, both were present in normal concentration. The concentration of lymphocytes varied directly with that of the monocytes, although it remained within normal limits throughout. The concentration of hemoglobin varied between 19 and 26 Gm. per 100 ml. during the acute illness, fell steadily to a low of 9 Gm. per 100 ml. at 43 days of age, and then slowly returned to normal without iron therapy.

On the third day of life, nose, throat, and blood cultures all revealed a pure growth of *Shigella alkalescens*. In vitro studies showed sensitivity of the organism to chloramphenicol, chlortetracycline, tetracycline, and streptomycin. It was resistant to erythromycin and penicillin. On the same day, chest and skull roentgenograms were negative, and the serum calcium was 8.3 mg. per 100 ml., the phosphorus 11.1 mg. per 100 ml., and the nonprotein nitrogen 48 mg. per 100 ml. The hemoglobin concentration was 19.8 Gm. per 100 ml.

On the sixth day of life, leukoagglutinins could not be found in the infant's serum nor was there any inhibition of starch granule phagocytosis with a mixture of infant's serum and donor white blood cells. The technique employed was that of Finch and Detre.[6]* The L. E. preparation was negative.

A second blood culture on the seventh day of life was sterile. The cerebrospinal fluid on this day showed moderate xanthochromia, no cells, a protein concentration of 97 mg. per 100 ml., and no growth on culture. A

*We thank Dr. Kathryn D. Detre for performing these studies.

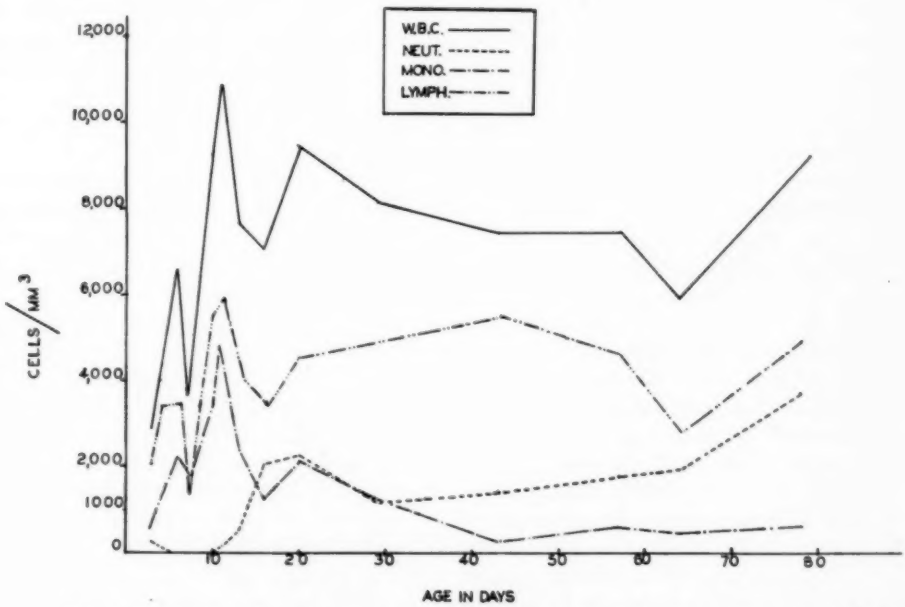

Fig. 1. Serial values for the concentration of white blood cells in the capillary blood of the patient. W.B.C. = total white blood cells. NEUT. = total mature and nonsegmented neutrophils. MONO. = monocytes. LYMPH = lymphocytes.

Table I. Serial values for hemoglobin and formed elements in the blood*

Age in days	3	4	6	7	10	11	13
Hemoglobin (Gm./100 ml.)	19.8		25.8	19.1			
White blood cells	2,900	4,050	6,600	3,700	9,350	10,950	7,750
Neutrophils, segmented	87	81	0	0	0	110	310
Neutrophils, band	145	0	0	0	0	0	233
Lymphocytes	2,146	3,402	3,564	1,406	5,610	5,913	4,185
Monocytes	522	405	2,244	1,739	3,640	4,818	2,480
Eosinophils	0	162	792	518	281	110	543
Basophils	0	0	0	37	0	0	0
Platelets (thousands)			105				
Reticulocytes (%)							

*Unless otherwise stated values indicate number of cells per cubic millimeter of blood.

bone marrow smear was also obtained on this day (Table II) and found to be slightly hypocellular, possible due to technique, with few megakaryocytes seen. The predominant cells were myelocytes. No polymorphonuclear neutrophils were present and this picture is that generally referred to as "maturation arrest." There was some increase in young monocytes. Another bone marrow study at 29 days of age revealed a cellular, normal marrow (Table II).

At the age of 8 days, the total serum proteins were 6.72 Gm. per 100 ml. with an albumin of 2.48 Gm. per 100 ml. and a globulin of 4.24 Gm. per 100 ml. The specific globulin fractions, determined by paper electrophoresis, were as follows: alpha$_1$ globulin, 0.67 Gm. per 100 ml.; alpha$_2$ globulin, 1.58 Gm. per 100 ml.; beta globulin, 0.94 Gm. per 100 ml.; and gamma globulin, 1.05 Gm. per 100 ml. An electroencephalogram performed on that day was read as within normal limits.

On the tenth day of life, stool cultures were taken and grew out *Escherichia coli*. On the same day the intramuscular administration of 5 units of aqueous corticotropin did not result either in the appearance of neutrophils in the peripheral blood or in a fall in the absolute eosinophil count.

The nonprotein nitrogen was 30 mg. per 100 ml. on the twelfth day of life.

At the age of 14 days the serum electrolytes were as follows: CO_2 content 22 mEq. per liter, chlorides 93 mEq. per liter, sodium 133 mEq. per liter, and potassium 5.7 mEq. per liter (hemolyzed). Further studies on that day revealed that the infant's blood type was O, DC positive, E negative, c positive, Kell and Duffy negative. The Coombs test, direct and indirect, was negative.

The mother's blood type was B, DC positive, E negative, c positive, Kell negative, and Duffy positive. Studies performed 29 days post partum revealed that her fasting blood sugar was 96 mg. per 100 ml. and her serum calcium and phosphorus were 12.1 mg. per 100 ml. and 4.5 mg. per 100 ml., respectively. On that day her platelet count (direct method) was 286,000 per cubic millimeter and her white blood count was 6,100 with 63 per cent neutrophils, 20 per cent lymphocytes, 14 per cent monocytes, and 3 per cent eosinophils.

At 15 days of age, the infant's urine showed an alpha amino nitrogen excretion of 24 mg. in 24 hours, which is within the normal range for a newborn.[7] The 17-ketosteroid excretion was 0.2 mg. in 24 hours. After the intramuscular administration of 5 units of corticotropin, it was 0.8 mg. per 24 hours. The 17-hydroxycorticoid excretion was 0.5 mg. per 24 hours. The above values for steroid excretion are all within normal limits.

When the infant was 8 months old, the mother's serum was demonstrated to agglutinate both the infant's and father's leukocytes.

DISCUSSION

Shigella alkalescens is considered to be a normal inhabitant of the human intestine,[8]

16	20	29	43	57	64	78	176	198	248	470
20.1	17.5	13.5	9.0	10.3	10.8	11.2	14.0	13.2	13.3	12.9
7,100	9,450	8,200	7,500	7,500	6,000	9,300	7,650	9,300	8,700	7,700
1,846	2,268	1,230	1,425	1,650	1,920	3,720	1,683	1,767	2,523	3,619
213	0	0	0	150	0	0	0	0	87	0
3,550	4,631	5,002	5,475	4,650	2,940	4,929	4,055	5,394	5,220	3,080
1,349	2,174	1,312	300	600	420	465	1,301	1,302	435	539
142	378	656	300	375	720	186	536	837	522	385
0	0	0	0	75	0	0	77	0		77
208	160	122	256						230	270
				3.3	1.4	2.4				

but convincing evidence for its occasional pathogenicity has been presented by Nabarro and Edward.[9] This organism has been cultured from the blood of patients with puerperal fever[10] and pyelocystitis.[11]

In the present case, the simultaneous isolation of *Shigella alkalescens* from the blood, nose, and throat and the infant's symptoms indicated a true infection. While an obvious portal of entry was not determined, it was felt that the microorganism most likely gained access to the infant's blood stream either via the placenta or by direct fecal contamination from the mother at the time of delivery. Unfortunately the bacteriologic studies on the mother were not done until she was almost 1 month post partum. This could account for the negative results since by then it is conceivable that an infection might have cleared spontaneously. It is also possible that the infection may have been acquired in the nursery by direct skin contact, but no studies were done on nursery personnel so this cannot be evaluated.

Although the infant manifested convulsions and tachypnea, he continued to feed well and his color remained good except for a short period of cyanosis. The normal concentration of protein in the cerebrospinal fluid of the newborn has not yet been defined.[12-14] Some clinics would consider that of our patient to be within normal limits although his symptoms suggest that a previous subarachnoid hemorrhage was responsible for the relatively high value. It is also possible that the seizures were a manifestation of neonatal tetany since low normal calcium concentrations in the range of that of our patient have been described in this condition[15]; the serum phosphorus of 11.1 mg. per 100 ml. is also suggestive. However, the latter value might be considered as almost within normal limits by Bruck and Weintraub.[16] Zetterstrom and Arnhold[17] found phosphorus values as high as 11.9 mg. per 100 ml. in infants born of diabetic mothers, without manifestation of tetany. The mother of our patient had a normal fasting blood sugar level. It would be reasonable to assume then that the infant's convulsions were due to any one of or a combination of the following factors: sepsis with an endotoxin-producing gram-negative rod, tetany of the newborn and, least likely, meningeal irritation due to subarachnoid bleeding.

The monocytosis accompanying the agranulocytosis in our case resembles that seen in several previously reported cases[2, 4] in which it occurred both with and without a demonstrable infection. There is no adequate explanation for this phenomenon but it is known to take place during recovery both from acute infections and from agranulocytosis.[18] It has been said to indicate a good prognosis in the latter.[19]

Sepsis of the newborn. Several series of cases of septicemia occurring in the newborn infant have been reported. Dunham,[20] in 1933, described 39 infants with neonatal sepsis in which hemolytic streptococcus was the most frequent agent. Two infants had mild leukopenia and died. In 1949, Silverman

Table II. Bone marrow studies*

	May 20, 1958	*June 11, 1958*
Megakaryocytes	Few	Few
Myeloblasts	2	11
Promyeloblasts	0	6
Myelocytes, neutrophilic	63	8
Myelocytes, eosinophilic	0	1
Metamyelocytes, neutrophilic	1	13.5
Metamyelocytes, eosinophilic	0	2.5
Band, neutrophilic	2	11.5
Band, eosinophilic	0	2
Polymorphonuclears	0	3
Eosinophils	1	3
Basophils	0	0
Lymphocytes, large	0	0
Lymphocytes, small	9	17.5
Monocytes	5	0
Pronormoblasts	0	3
Normoblast 1	2	3
Normoblast 2	0	5.5
Normoblast 3	15	9.5

*Performed on marrow aspirated from the tibia (200 cells counted).

and Homan[21] presented a series of 25 newborn infants with sepsis. In 17 cases, the responsible agent was an enteric microorganism. One infant with *E. coli* sepsis had a severe leukopenia and died. Nyhan and Fousek[22] recently reported a series of 106 newborn infants with sepsis. Leukopenia was noted in 5 patients, *E. coli* being the infecting agent in 1, and group A streptococcus in 4. Clifford,[23] in 1947, discussed septicemia in the mother and stressed the possibility of transplacental infection of the infant.

It is of interest that in the above-reported series, leukopenia is not a common occurrence and complete absence of circulating neutrophils is not mentioned. Similarly, in none of these cases was *Shigella alkalescens* the offending organism.

No correlation could be made between the levels of the leukocyte counts and the specific invading microorganism.[22]

Neutropenia. The syndrome of agranulocytosis, described in 1922 by Werner Schultz,[24] consists of severe sore throat, necrotic lesions, prostration, extreme reduction or even complete disappearance of granulocytes from the blood, and, in rapid succession, sepsis and death. Since the term "agranulocytosis" specifically refers to the above syndrome, we have utilized the words "neutropenia" and "granulocytopenia" in the case presented, even though there was complete absence of the circulating neutrophils from the sixth to the eleventh day of life.

The simultaneous occurrence of neutropenia and *Shigella alkalescens* sepsis, in this infant, suggests a causal relationship. Neutropenia has been seen in infections involving enteric organisms, brucellosis, influenza, measles, rubella,[25] and *Pseudomonas aeruginosa*.[26]

Smith and associates[27] have suggested that *neutropenia of infection* may be due to the effect of endotoxin released as the gram-negative bacteria disintegrated and, indeed, administration of purified endotoxin has resulted in transient leukopenia and granulocytopenia.[28] Others have concluded that localization of the organisms in the bone marrow may initiate the neutropenia.[26] In Schümer's case, described above, bone marrow study revealed complete absence of the myelocytic series. Our patient demonstrated an abundance of myelocytes in the marrow, suggesting that the mechanism of production of his agranulocytosis differed from that of Schümer's patient. Although agranulocytosis is known to precede and indeed to predispose to the development of infections, it is felt that the occurrence of neutropenia in the present case was the result of infection rather than the cause. Neutropenia has been shown to be fairly characteristic of infections with gram-negative, enteric organisms.[25] The early onset of symptoms at 24 hours of age, the simultaneous isolation of the microorganism from the nose, throat, and blood, and the progressive neutropenia leading to a complete absence of circulating neutrophils at 6 days lend weight to the impression that sepsis preceded and initiated the granulocytopenia. Furthermore, the natural habitat of the organism and its relatively low pathogenicity favor the possibility of contamination at the time of birth.

Transient granulocytopenia of the newborn. This term, as used by Lehndorff,[2] is

described in the introductory paragraph. As in the present case, both of his patients demonstrated a monocytosis in the blood and a pattern of maturation arrest at the neutrophilic myelocyte stage in the marrow. The author felt that this entity represents a toxic-allergic neutropenia of the newborn. Luhby and Slobody,[3] describing the same cases, postulated transplacental isoimmunization to a leukocyte factor, but a search for leukoagglutinins in the mother's serum was unrevealing. The present case would seem to fit into this syndrome with the additional distinguishing features that two possible etiological agents have been demonstrated: sepsis and maternal leukocyte agglutinins.

Chronic, benign neutropenia of infancy and childhood. This syndrome was reviewed by Stahlie in 1956.[29] Thirteen of the 16 reported cases resulted in spontaneous hematologic cure as late as 4 years after onset. The youngest patient was 5 months old and the oldest 6 years. The etiology is unknown. The chronicity of this disease, the geographical predilection for Europe, and the age at onset are not characteristic of the case presented and would exclude this disease as a diagnostic possibility; furthermore, injection of ACTH in the present case did not result in the appearance of neutrophils peripherally as it did in Stahlie's case.

Infantile genetic agranulocytosis. This was also considered. Kostmann,[30] in 1956, described 14 children in nine families all but 2 of whom died as a result of this disease. There was consanguinity between parents in five of the involved families. The patients manifested a maturation arrest of the bone marrow similar to that in our case. Luhby and co-workers[31] in 1957 described an infant who presented with umbilical stump cellulitis and agranulocytosis at 2 weeks of age. The child died of overwhelming infection at 7 months. The authors concluded that this case represented a congenital genetic agranulocytosis due to an inborn error of development and maturation of the neutrophils. The condition does not appear to have existed in the present case since, although it can occur at birth, it is unremitting and does not result in spontaneous cure.

Transitory congenital neutropenia. Recently Stefanini and his associates[32] described 2 leukopenic mothers who each gave birth to severely neutropenic infants. The bone marrow in the leukopenic mothers as well as in the infants showed hyperplasia and maturation arrest of the granulocyte series. The white blood counts of both infants returned to normal levels after 4 weeks. In 1 case the mother's serum contained a demonstrable leukoagglutinin which could be transferred by transfusion to a normal person. In both instances neutropenia was considered most likely due to the transplacental passage of a neutropenic factor.

This new clinical entity differs from the case reported in that both mothers had a chronic idiopathic neutropenia of presumed immune origin and in the length of time required for the return of the infant's white blood counts to normal.

Isolated chronic neutropenia. Isolated chronic neutropenia can sometimes precede a more generalized failure of marrow function and may result in acute leukemia, aplastic anemia, or myelomatosis.[25] The latent period may average several months to 2 years. The bone marrow may be aplastic, hyperplastic, or normal, and hyperplasia, when observed, has been characterized by a "maturation arrest" at the myeloid stage of the leukocytes.[33] The early onset and transient nature of the agranulocytosis in the present case would rule out this diagnosis.

Splenic neutropenia. In this syndrome, there is thought to be excessive destruction of granulocytes by the spleen. It can be primary or secondary to such diseases as Banti's syndrome, Felty's syndrome, Gaucher's disease, sarcoidosis, and Hodgkin's disease.[25] The continued good health of the infant, and the transient nature of the splenomegaly and neutropenia rule out this disease.

Chronic idiopathic immunoneutropenia. This has been recently established as a hematologic entity in which the formation of autoantibody against the patient's own neutrophils has been demonstrated. This may

result from drug sensitivity, from inflammatory processes (e.g., viral pneumonia, lupus erythematosus), or may be of unknown origin.[34] In the case presented, no leukoagglutinins were demonstrated in the infant's serum.

Recurrent, cyclic, or periodic neutropenia. This syndrome can develop within the first year of life.[35] The present patient had no recurrences so that this was excluded as a diagnostic possibility.

A possible mechanism for the production of agranulocytosis in the present case. Craddock and co-workers[36] have demonstrated, in dogs, the existence of a "myeloid reserve" consisting of stores of neutrophils which can be rapidly released from the bone marrow into the circulation. The size of this reserve is many times larger than the total number of circulating leukocytes. When infection or other inflammatory agents increase the peripheral utilization of leukocytes, the immediate need is met by this reserve and the peripheral leukocyte level seems related to its size. According to Craddock and co-workers,[37] overwhelming infection "imposes a sudden, massive, and continuing demand for leukocytes on a marrow probably not entirely normal from a functional standpoint." It has been shown that bacterial endotoxin may have a direct cerebral effect and an affinity and toxicity for leukocytes,[38] although Donald and co-workers[39] recently demonstrated on dogs that neither the brain nor the adrenal glands are necessary for the induction of neutropenia by toxin. Thus, it may be postulated that in our patient excessive peripheral utilization of leukocytes, coupled with a functional impairment of their maturation in the marrow, resulted in depletion of the myeloid reserve and in a consequent absence of neutrophils from the peripheral circulation. Improvement did not occur until the reserve was replenished which required several days.

It is difficult to evaluate the later discovery of maternal leukoagglutinins against the infant's and father's leukocytes. It has been shown that leukoagglutinins can occur in the sera of pregnant women who have never received a blood transfusion[32, 40] Recently Lalezari[3] described a family in which there were several cases of neonatal neutropenia. The maternal serum showed potent leukoagglutinins active against cells of all her living children and her husband. They suggested that this represents a condition involving neutrophils which is analogous to hemolytic disease of the newborn. Some investigators state that maternal leukoagglutinins have not shown a consistent effect on the newborn, and that little is known of their clinical significance except that they can produce transfusion reactions.[40] Stefanini[32] makes the following statement: "It should not be concluded that the presence of a demonstrable leukopenic factor in the mother's blood is necessarily followed by its passage through the placenta and by the birth of neutropenic children."

It would seem logical therefore to assume that the neutropenia in this case was secondary to sepsis due to *Shigella alkalescens* resulting from transplacental infection or maternal fecal contamination shortly preceding birth. In addition, maternal leukoagglutinins most likely were present at birth and may possibly have crossed the placenta and thus contributed to the peripheral sequestration of circulating leukocytes.

SUMMARY

A newborn infant with granulocytopenia and sepsis caused by *Shigella alkalescens* is presented. Eight months post partum the mother's serum was found to contain agglutinins against the neutrophils of both the baby and the father. It is concluded that the granulocytopenia was probably secondary to sepsis caused by *Shigella alkalescens* resulting from transplacental infection shortly preceding birth, or from direct maternal fecal contamination, and that sequestration of neutrophils by transplacentally acquired maternal leukoagglutinins may also have contributed to the granulocytopenia.

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Bacillus faecalis alcaligenes septicemia in the newborn

S. A. Doxiadis, M.D.,* M. Pavlatou, M.D., and O. Chryssostomidou, M.D.

ATHENS, GREECE

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BACILLUS *faecalis alcaligenes* is a common nonpathogenic inhabitant of the human colon, which infrequently becomes pathogenic and is responsible for clinical disease.

Hirst[1] in 1917 isolated *Bacillus faecalis alcaligenes* from the blood of 18.7 per cent of patients with prolonged pyrexia; he was the first to suggest that this organism may become pathogenic to man when there is underlying disease of the intestine which permits invasion of the blood. Following this suggestion, Webster[2] in Australia found *Bacillus faecalis alcaligenes* in the blood of 3 of 11 nursing infants who developed severe diarrhea with blood in the stools.

Since then there have been isolated reports of septicemia, meningitis, or a combination of both due to *Bacillus faecalis alcaligenes.* Weinstein and Wasserman[3] in 1951 reviewed the literature on all the morbid manifestations of infection with *Bacillus faecalis alcaligenes* and added a case of their own. In the last 8 years a few more cases of illness due to this organism have been reported, mostly in adults.[4-8]

In the neonatal period and in early infancy infection with *Bacillus faecalis alcaligenes* has occurred as septicemia with meningitis[9, 10]; in the literature available to us we could not find reports of septicemia without meningitis due to this organism in this age period.

In the newborn and premature infant unit of the State and University Maternity Hospital "Alexandra" in Athens during the years 1956-1959, we observed 33 cases of infection due to *Bacillus faecalis alcaligenes* in which this organism was isolated from the blood. Thirty of these babies had in addition to the signs of a generalized infection a peculiar manifestation on the skin which at first was diagnosed as erysipelas and which was so characteristic that it enabled us, when we became familiar with this phenomenon, to make the tentative diagnosis of *Bacillus faecalis alcaligenes* septicemia before the result of the blood culture became known.

MATERIAL

The material of the present study consists of 33 newborn infants with positive blood cultures for *Bacillus faecalis alcaligenes.* During the same time we observed 5 additional infants who had similar skin manifestations but whose blood cultures revealed other

From the State and University Maternity Hospital Alexandra.

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**Address, 3 Neophytou Vamva St., Athens, Greece.*

organisms: in 2 these were *Pseudomonas aeruginosa,* in 2, *Escherichia coli,* and in 1, Proteus.

In addition, we have also observed 16 newborn infants with the same cutaneous lesion, but in whom blood cultures were not obtained.

BACTERIOLOGIC METHODS

Five to ten milliliters of venous blood was inoculated into 50 to 100 ml. of tryptose broth and incubated at 37° C. If growth was obtained, a subculture was made on a blood agar plate for isolation and identification of the organism. In the 33 cases of the present series a gram-negative bacillus was isolated which has been identified as *Alcaligenes faecalis.* The isolated organism showed the following characteristics:

Morphology and staining reactions. Gram-negative, non–spore forming, motile bacillus.

Culture. It grows readily on all ordinary media; is aerobic; in broth it produces a homogeneous clouding and later a pellicle is formed. On nutritive agar it forms round, smooth colonies which are raised with undulated edges.

Fermentation reactions and other biochemical properties.

1. Metabolism of sugars was tested by inoculation of the isolated strain into a series of tubes containing peptone water and 0.5 per cent of one of the sugars listed below or alcohol. Bromothymol blue was used as an indicator. All the isolated strains failed to ferment glucose, mannitol, sorbose, sorbitol, dulcite, lactose, maltose, saccharose, trehalose, inositol, salicine, xylose, arabinose, adonitol, or ramnose. The action on glycerol was tested on Stern's glycerol medium. All strains failed to attack glycerol.

2. Action on salts of organic acids: to test the ability of the isolated strains to utilize sodium citrate as the sole source of carbon, Simmons' medium was used. All the isolated strains were "citrate positive."

3. Urease formation: Christensen's medium was used. A negative reaction was obtained with all strains.

4. Indol formation: The Kovacs reaction was negative with all the strains.

5. Gelatin liquefaction was not caused by any of the strains.

6. Reductive actions: (a) The ability to produce hydrogen sulfide was tested by growing the strain on lead acetate agar. None of the strains formed H_2S. (b) None of the strains reduced nitrate salts to nitrites. (c) None of the strains reduced neutral red.

7. Voges-Proskauer reaction and methyl red test: The Voges-Proskauer reaction was tested with alpha-naphthol and potassium hydroxide in a 3 day culture in Clark-Lubs medium. All the isolated strains failed to produce acetylmethylcarbinol. The methyl red reaction was also negative.

8. Litmus milk was not coagulated but it was rendered strongly alkaline.

9. Braun's (KCN) reaction was negative with all strains.

10. Phenylpyruvic acid (Henriksen) was negative with all strains.

Table I. Weight at birth and mode of delivery of 35 infants (23 boys and 10 girls)

Weight at birth	
Under 1,500 grams	5
1,501 - 2,000 grams	2
2,001 - 2,500 grams	9
Over 2,501 grams	17
Total	33
Delivery	
Normal (including 5 breech presentations)	25
Forceps	6
Cesarean section	2
Total	33

RESULTS

The sex, weight at birth, and mode of delivery of the infants are shown in Table I.

As may be seen from Table I there was a preponderance of boys. Half of the infants were premature, and there was a higher proportion of forceps deliveries than in the usual hospital practice.

Condition at birth. The condition of 18 babies at birth was not satisfactory. This was attributed to hypoxia since the main signs

Table II. Initial localization of red patches

	No. of patients
Face	6
Neck	8
Groins	2
Buttocks	3
Abdomen	5
Abdomen and thigh	1
Face and chest	1
Ankles	1
Neck and thigh	1
Face, neck, and abdomen	1
Total	29

were cyanosis, difficult or grunting respiration, and retractions of the intercostal spaces, of the epigastrium, and of the supra- and infraclavicular areas. In addition to the manifestations of hypoxia in 3 of the 6 babies born by forceps delivery, there were signs of intracranial irritation. As these 18 babies were ill before the onset of the septicemia it was difficult to determine the time of onset of the generalized infection and what signs, except the cutaneous manifestations, could be attributed to it.

Feeding. All affected babies were partly or wholly artificially fed.

Clinical manifestations. Fifteen babies were in good condition at birth or their condition became good after a transient and mild respiratory difficulty. In these babies any clinical signs were attributed to the septicemia. However, autopsies on 3 of them revealed other lesions (subarachnoid hemorrhage in 2 and a severe congenital malformation of the heart in 1) unrelated to the septicemia. Thus there were 12 babies in whom there was no other illness than the septicemia due to *Bacillus faecalis alcaligenes.* In these babies the general signs of illness were not different from those of other generalized infections in the neonatal period. Listlessness and reluctance to take feedings were present in all except 2 babies, 3 had cyanotic attacks, 2 had periods of apnea, and 2, convulsions. The temperature was significantly elevated in 4 cases. It is important to note that only 2 of the 33 babies had diarrhea.

The peculiar red areas on the skin mentioned above were observed in 29 of the 33 newborn infants who had positive blood cultures for *Bacillus faecalis alcaligenes.* In 10 of these there was no evidence of other illness. This skin manifestation was the first and only sign of generalized infection in 2 of these babies, both of whom were immediately treated with chloramphenicol and survived. In the other 8 babies the above-mentioned general manifestations either preceded the appearance of the skin manifestation by 24 hours or appeared on the same day.

The peculiar areas appearing on the skin were bright red and well demarcated, with a diameter of at least 4 cm. Their shape was irregular and it often changed from day to day, sometimes from hour to hour. Usually they increased in size for a day or two and then began to fade. In some cases new erythematous patches appeared in other parts of the body. Fading of the lesion was not always a good prognostic sign, since it was seen in babies whose condition deteriorated and who died.

The areas of the surface of the body initially affected are shown in Table II; the face and neck were the most frequently affected areas.

In 3 cases a section of the skin was taken a few hours after death from an area exhibiting the typical redness during life and examined histologically. There were no detectable changes.

Blood examination. The white blood cells were counted in 5 cases only. In 3 the total white blood count was below 10,000 per cubic millimeter but with a definite preponderance of the myeloid series. In the remaining 2 infants the white blood count was 27,000 and 48,000 per cubic millimeter, most of the increase being due in each case to myeloid cells.

Treatment. All strains of *Bacillus faecalis alcaligenes* cultured from the blood were tested for their sensitivity to antibiotics. They were insensitive to all antibiotics tested.

In spite of these results antibiotics were given to all babies. Some of them, especially the first cases, received penicillin and strepto-

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mycin because the redness of the skin was thought to be erysipelas. Other babies received one of the tetracyclines. All except 5 received chloramphenicol at some stage of their illness because there was the impression that it was the antibiotic most likely to help. From the present material no positive proof can be obtained that it had any effect or any better effect than the other antibiotics.

Course and outcome. Of the 33 babies, 20 died. Death occurred between 12 hours and 11 days from the appearance of the red patches.

In one case of a baby who developed meningitis 5 days after the appearance of the skin lesions, *Bacillus faecalis alcaligenes* was grown from the cerebrospinal fluid. The baby survived but developed hydrocephalus.

Autopsy was performed in 8 cases. In 2 there was severe malformation of the heart, in one hyaline membrane disease, and in 2 intracranial hemorrhage. There were also inflammatory changes in the lungs of 3 infants and suprarenal hemorrhage in one. These were possibly connected with the generalized infection. The findings which could be attributed with certainty to the septicemia were purulent pericarditis in 2 cases and meningitis in one.

ILLUSTRATIVE CASES

Case 1. This baby, who weighed 1,350 grams at birth, was well till the third day of life when an erythematous lesion appeared on the face. The following day (Fig. 1) new lesions had appeared on the lower abdomen and on both thighs. The blood culture was positive for *Bacillus faecalis alcaligenes.* The baby died on the sixth day. After death the redness of the skin faded.

Case 2. A female infant, weighing 3,590 grams, was born by breech delivery after an uneventful pregnancy. At birth there was edema and bruising around the buttocks, cyanosis, and grunting respiration. After a few hours she was very restless and uttered a high pitched "cerebral" cry. The third day the baby became very listless and refused food, and the breathing was superficial and rapid. Blood culture was taken which showed the presence of *Bacillus faecalis alcaligenes.* She was given penicillin and streptomycin and there was a slight improvement, but 2 days later the typical red patches appeared on the buttocks and the legs and her condition deteriorated. Erythromycin was substituted for the other antibiotics but in spite of oxygen and other supportive therapy the baby's condition gradually grew worse and

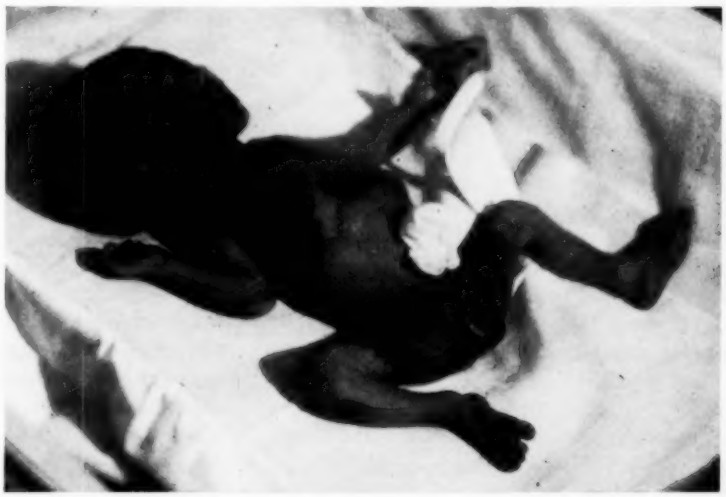

Fig. 1. Erythematous lesions on face, lower abdomen, and both thighs of 4-day-old infant.

she died on the eleventh day of life. At autopsy there was thick pus in the pericardium, extensive hemorrhage in both suprarenal glands, and a small subarachnoid hemorrhage. Since the autopsy was performed 12 hours after death the pus from the pericardium was not cultured.

Case 3. A male infant, birth weight 2,340 grams, had a normal delivery and was in good condition after birth. On the fourth day of life the baby developed grunting respiration and cyanosis. A few hours later the typical red areas appeared on the chin, the neck, and the upper half of the chest. Blood culture showed the presence of *Bacillus faecalis alcaligenes.* Chloramphenicol was given in doses of 60 mg. per kilogram of body weight per day but the baby's condition deteriorated and the following day there were new red areas on the groins and the beginnings of scleredema on face and thighs. Chloramphenicol was given parenterally and the general condition improved with disappearance of the redness and the scleredema. On the ninth day of life, however, the general condition deteriorated again and new brown-red patches appeared on the lower abdomen and the groins. As the baby's condition became worse from day to day chloramphenicol was stopped and penicillin and streptomycin were given parenterally. On the fourteenth day of life, i.e., 6 days after the relapse, the baby became desperately ill with grunting respiration, generalized scleredema, and increased tonus of the neck and upper extremities and died the following day. During the whole of his illness the temperature was below 37° C., the total white blood count was elevated between 20,000 and 48,000 per cubic millimeter, and the stool culture was negative for any pathogens. At autopsy the surface of both hemispheres of the brain was covered with a thin purulent yellow-green exudate. There were also small petechial hemorrhages and hyperemia of the brain. Culture of the pus was not done because again many hours had elapsed after death.

Case 4. A female infant was delivered by forceps with a birth weight of 3,470 grams. After delivery the general condition was poor, the baby being very tired, with tachypnea, respiratory distress, and upturning of the eyes. Penicillin and streptomycin were given parenterally and the following day chlorpromazine was added because she was very restless. For the next 3 days the signs of cerebral irritation persisted and there were even mild generalized convulsions for which phenobarbital and chloral hydrate were given. On the seventh day of life the first redness appeared on the face, extending to the neck, and a few hours later another red patch was seen on the left knee. The blood culture grew out *Bacillus faecalis alcaligenes,* and chloramphenicol administration was started immediately. Four days later the red patches faded; the baby appeared better and, the extremities became less spastic. The following day, however, the spasticity increased and a slight bulging of the anterior fontanel led to examination of the cerebrospinal fluid. This was purulent with 14,000 white blood cells per cubic millimeter, a protein content of 1.9 Gm. per 100 ml.; spinal fluid culture showed the presence of *Bacillus faecalis alcaligenes.* Sulfadimetine was added to the treatment and given for 14 days. Chloramphenicol was discontinued after 10 days. On the seventeenth day, i.e., 5 days after the onset of the meningitis, the cranial sutures appeared to separate and the head circumference was 37 cm. The fontanel was still bulging, opisthotonos was present, and spinal taps were done to relieve the pressure. The general condition of the patient for the following month remained unchanged with restlessness at times, occasional generalized convulsions, and failure to gain weight. On the forty-sixth day the cerebrospinal fluid contained 120 white blood cells per cubic millimeter and 0.1 Gm. of protein per 100 ml. but it was sterile. However, 9 days later the baby started vomiting and losing weight and although the culture of the cerebrospinal fluid did not reveal any organisms the white blood cells and protein in the spinal fluid were increased. Polymyxin, 8 mg. daily, was given intramuscularly for 6 days and examination of the cerebrospinal fluid on the

day following cessation of treatment (the fifty-seventh day) showed only 80 white blood cells per cubic millimeter, protein 0.66 Gm. per 100 ml. and sugar 0.047 Gm. per 100 ml. *Bacillus faecalis alcaligenes* grew out in the culture at this time. The baby left the hospital on the fifty-ninth day of life with a bulging fontanel, slight separation of the sutures, spasticity of the limbs, a head circumference of 40.4 cm., and failure to gain weight. Unfortunately this baby did not come back for a follow-up and could not be traced.

As was to be expected, an important factor in determining the outcome was the presence of any associated illness and above all of hypoxia or intracranial birth injury. Thus, of the 12 babies who showed during life no other illness or abnormality, 7 survived, while of the 21 in whom we found, either during life or at autopsy, hypoxia, birth trauma, or severe congenital malformation, only 6 survived.

DISCUSSION

We cannot explain the high incidence of *Bacillus faecalis alcaligenes* septicemia in our newborn and premature baby unit. While only occasional cases in newborn babies have been reported in the literature and these always in association with meningitis, we have isolated this organism from the blood of 33 babies within a period of 4 years.

During this time about 24,000 babies were born at our Hospital. Even within these 4 years there has been an irregular distribution of cases. Thus 32 were seen in the first 3 years and only one in the fourth. Hirst[1] suggested that this organism may invade the blood stream when the intestine is not functioning properly as in cases of diarrhea. This explanation does not apply, however, in our material because only 2 of the 33 babies had diarrhea before or at the time of septicemia. The possibility of a particularly virulent strain spreading from one infant to another can also be excluded because although the septicemia occurred twice in infants of the same nursery and at about the same time, in all the remaining cases this was an isolated occurrence, in both time and locality. It is possible that this type of septicemic illness is more common than is presently believed in newborn infants and if blood cultures are not done on a large scale it may be missed. This explanation again does not appear to be wholly satisfactory because it is to be expected that in the case of a seriously ill baby, a blood culture, among other investigations, will be done in most cases.

We have not found any previous description of the peculiar skin manifestations seen in 29 of our 33 babies. These red areas were at first thought to be erysipelas and it was only when penicillin failed to influence the course of the disease that we started looking for other causes. The red color is obviously due to hyperemia which appears to be a local vasomotor phenomenon and not true inflammation of the skin. The histologic examination of the affected skin done in 3 cases shortly after death which did not show any changes is in favor of this conception as is the rapid alteration in shape and size of the red areas. It is of interest that Miles[11] described a condition in frogs called red-leg, which is due to *Bacillus faecalis alcaligenes* and *Proteus hydrophilus*. The clinical description of red-leg, however, does not give the impression of a vasomotor phenomenon but rather of an acute inflammation.

The dilatation of the vessels of the skin of certain areas may be due to an endotoxin, although it is not possible to explain why some areas are affected and not others. Whatever the pathogenesis of this skin manifestation may be, it has proved a very useful diagnostic sign, since it enabled us to suspect the presence of *Bacillus faecalis alcaligenes* septicemia before the result of the blood culture became known. It should not, however, be considered as a pathognomonic sign since, as it has been already said, the same clinically undistinguishable skin manifestation was seen in 5 infants with septicemia due to other organisms. It may be that this is a nonspecific vasomotor reaction due in the majority of cases to one causative agent.

One is reminded of the erythema nodosum, which, although a nonspecific lesion, was due at one time and in certain countries almost always to a primary tuberculous infection. It will be of great interest to learn of similar observations of the occurrence of these very characteristic skin manifestations in septicemic illnesses of the newborn infant in other centers.

SUMMARY

1. The present paper describes the bacteriologic and clinical features of 33 newborn infants suffering from septicemia due to *Bacillus faecalis alcaligenes.*

2. In 29 of these infants erythematous lesions resembling erysipelas appeared on large areas of the skin. This is considered a nonspecific vasomotor phenomenon. It is not pathognomonic for *Bacillus faecalis alcaligenes* septicemia since it was also seen in 5 infants suffering from septicemia due to other organisms, but it is of great help in the initial diagnosis of this septicemic illness since it was present in 88 per cent of the cases.

3. All isolated strains of *Bacillus faecalis alcaligenes* were resistant to sulfonamides and all antibiotics tested; consequently there was a high mortality rate; 20 of the 33 infants died in the neonatal period.

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A familial convulsive disorder with an unusual onset during intrauterine life

A case report

M. K. Badr El-Din, M.D.

ALEXANDRIA, EGYPT, U.A.R.

A GENETIC neurological disorder has been observed in which convulsive attacks apparently occurred in utero. No references to intrauterine convulsive attacks have been found in the literature.

S. A. A., a white female infant, aged 17 days, was first examined on Dec. 28, 1957, because of repeated convulsions, which apparently were the continuation of intrauterine seizures first noticed by the mother when she was five months pregnant. At first, she felt the quickenings were more powerful than usual. The recurrent movements gradually increased in force and duration and resembled convulsions. These prenatal attacks occurred so frequently that the mother predicted that her expected child would be abnormal. She had experienced similar intrauterine movements with previous pregnancies.

The baby was born of the fourth pregnancy; she was the third sibling to have the disorder. The following is a short summary of the history of the previous siblings:

First child. A male infant died at age 12 months of acute gastroenteritis. There was no history of convulsions either in utero or after birth, and the development was normal.

Second child. A male infant died at the age of 10 months in status epilepticus. Intrauterine convulsions had been felt by the mother, and the infant had repeated attacks after birth. He was able to recognize his parents; he sat when 5 months old, but never crawled.

Third child. A female infant with a history of repeated convulsions that started during fetal life died when 3 months of age in status epilepticus.

The parents are first cousins. Two sisters of the wife (*IV, 6* and *8*) married to two brothers of the husband (*IV, 5* and *7*) have given birth to siblings with the same disorder (Fig. 1).

S. A. A. was born at term, and delivery was unremarkable. There was no cry at birth, and the baby was cyanotic. Convulsions occurred immediately after birth, and there were recurrent convulsions subsequently. The baby was breast fed.

At the time of examination the infant weighed 2,800 kilograms and had a crown-heel length of 46 cm. The circumference of the head was 34.5 cm. There was generalized hypertonus of the entire body with a flexion attitude. On tapping over the chin or any

From the Department of Pediatrics, Alexandria University.

Address, Awkaf Bldg., Block D, Chatby, Alexandria, Egypt, U.A.R.

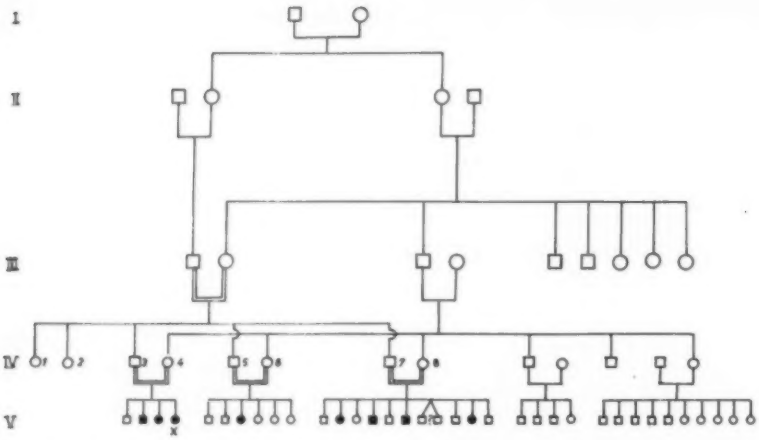

Fig. 1. Pedigree of family of S. A. A. Males indicated by squares, females by circles. Affected members indicated by solid symbols. × indicates the infant reported.

part of the body, a shocklike reflex extension of both upper and lower limbs occurred. No abnormalities were noticed in the chest, heart, or abdomen.

A convulsive episode occurred during examination. This began with a cry followed by risus sardonicus and a clonic convulsion lasting for 30 seconds. This was succeeded by a tonic seizure lasting approximately one minute. Cyanosis was extreme. After the seizure, complete flaccidity occurred and the infant went into deep sleep. Epanutin therapy was started.

Clinical course. The infant was re-examined on April 15, 1958, at the age of 4 months. The fits were reported to be somewhat less frequent and purely tonic (Fig. 2).

Fig. 2. Photograph of S. A. A., at the age of 4 months, during an attack.

The weight was 3,600 kilograms; the length, 52 cm., the anterior fontanel, 0.5 by 0.5 cm., and the head circumference, 37.5 cm. She could hold her head erect. Tapping over the chin produced the extensor attitude of all limbs.

A roentgenogram of the skull showed no calcification. The cerebrospinal fluid was normal, and the urine did not reveal phenylpyruvic acid. The Wassermann reaction was repeatedly negative.

The infant was last seen on April 24, 1959, at the age of 16 months, with a history of cough for one week and fever of one day's duration. Convulsive episodes were reported to have been less frequent with an average occurrence of one or two per week.

At this time she weighed 6,300 kilograms; the length was 62 cm., and the anterior fontanel was closed. The circumference of the head was 42.5 cm. There was a convergent strabismus. The two upper and lower central incisors were erupted. She had lost one of the lower incisors and the other one was loose. She could sit alone but could not crawl. She could say one or two indistinct words. On tapping over the chin, the reflex extension of limbs could not be elicited.

A convulsion occurred during this examination. It began with a cry from a par-

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tially spasmodic larynx with inspiratory stridor, followed by complete spasm, deepening cyanosis, and a tonic fit that lasted about 40 seconds. This was followed by sudden collapse. There was respiratory arrest and the heart rate became very slow. After 30 seconds, gaspings started, and the heart rate gradually increased. She became extremely flaccid and fell asleep.

Examination of the chest revealed bronchopneumonia. Therapy with Terramycin was instituted. The next day she died in status epilepticus. A postmortem examination was not performed.

DISCUSSION

An unusual neurological disorder has been observed which affected siblings of three related families. Three of 4 siblings were affected in the first family, one of 6 in the second family, and 4 of 12 in the third family. Both male and female siblings were affected. The members of Families I and II married to nonrelatives were not affected with this convulsive disorder (Fig. 1). Thus, it is evident that the disease is inherited and that the trait is recessive and not sex-linked.

The clinical pattern was similar in all affected infants. The chief manifestations were generalized rigidity, physical and mental retardation, reflex myoclonus, and repeated episodes of clonic and tonic seizures. The onset of convulsions in utero was characteristic. To my knowledge, this has not been described previously. The mothers could foretell during pregnancy whether the expected child would be normal or abnormal.

The disease was progressive; resistance to infection was low, and all of the affected children died in infancy. The maximum length of life was 16 months.

In the differential diagnosis the syndromes of congenital rigidity and of severe congenital quadriplegia should be considered. In both, muscle spasm is apparent early in life, and tonic and clonic convulsions are quite common and can be provoked by minor stimuli. However, there is no known observation of intrauterine convulsions or reflex myoclonus in these disorders.

The many diseases categorized as heredofamilial and degenerative diseases of the nervous system can be excluded as the victims are almost always quite normal at birth. Lundborg[1] described paramyoclonus multiplex in infants which was characterized by sudden shocklike contractions of the muscles resembling the reflex myoclonus in our cases. In Lundborg's cases, however, the myoclonus slowly became increasingly severe, whereas in time this disappeared in our case.

Krabbe's syndrome of cerebral sclerosis is strongly familial and occurs in infancy. It is characterized by rigidity and tonic and clonic convulsions that are easily provoked by external stimuli. Unlike our patients, however, the infants are considered to be healthy at birth and it is only when they have reached 4 to 6 months of age that the disease is manifest.

In status demyelinisatus of Vogt and Vogt,[2] in which there is progressive degeneration of the lenticular nucleus, the disease begins in infancy and is familial. It is characterized by rigidity, athetosis, tonic seizures, and dementia. The infants are, however, normal at birth and the course is slowly progressive, death usually occurring between the ages of 5 and 15 years.

At present the disorder described here cannot be classified under any known clinical entity and may represent a previously unrecognized genetic syndrome.

SUMMARY

An apparently new congenital nervous disease is described. It is heredofamilial and is characterized by physical and mental retardation, generalized hypertonus, reflex myoclonus, and convulsions which have their onset during intrauterine life.

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Congenital absence of the pituitary gland

Joseph D. Reid, M.D., M.R.C.P.E.*

KINGSTON, ONTARIO

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CONGENITAL absence of the pituitary gland in the presence of a normally developed brain is a rare anomaly. Since June, 1956, two cases have been reported independently by Blizzard and Alberts,[1] and by Brewer.[2] There appear to have been no cases in the neonate reported prior to 1956. This report will present a third case, compare the clinical features of these 3 cases, and attempt to evaluate the role of the pituitary gland in development of the fetal glands and of secondary sex characteristics in the human being.

CASE REPORT

M. M. (Autopsy No. 8577, Babies Hospital, New York), a full-term white boy, was born in another hospital at 1 A.M., May 5, 1957, of healthy parents. The pregnancy was said to be normal but details of antenatal care are not available. At 8 A.M. jaundice was noted; the infant was then admitted to Babies Hospital. Physical examination revealed a markedly icteric edematous newborn infant with cyanotic nails and lips. Respirations were 40 per minute, shallow, and irregular. The pulse rate was 94 per minute. He weighed 4,050 grams. A harsh systolic murmur was heard to the left of the sternum. The liver and spleen were palpable 2 to 3 cm. below the costal margin.

Laboratory investigation. The infant's blood group was A, Rh positive, and his hemoglobin level 15.9 Gm. per 100 ml. The mother's blood group was O, Rh positive. The Coombs test on the infant's blood was 2 plus positive. The patient's blood film showed many nucleated red blood cells. His serum bilirubin level shortly after admission was 14 mg. per 100 ml.

Course. At 3 P.M. he stopped breathing but responded to resuscitation. An exchange transfusion was started with group O, Rh positive blood, but after 200 c.c. was exchanged the respirations stopped and the heart slowed. The serum bilirubin level had fallen to 11.5 mg. per 100 ml. He had repeated periods of apnea and died at the age of 19 hours. The clinical diagnosis was erythroblastosis fetalis due to A-O incompatibility based on the jaundice, the mother's and infant's blood groups, and the positive Coombs test on the baby's blood.

Autopsy report. The infant weighed 3,900 grams and was 49 cm. in length. He was well developed and well nourished with marked icterus of the skin and conjunctivae. The

From the Department of Pathology, College of Physicians and Surgeons, Columbia University, and the Babies Hospital, New York, N. Y.

**Present address, Hotel Dieu Hospital, Kingston, Ontario, Canada.*

fingernail beds were cyanotic and the hands and feet were mildly edematous. Both testes were palpable in the scrotum. The heart was normally developed and weighed 25 grams. There was some dilatation of the right ventricle. The ductus arteriosus was widely patent and measured 2 cm. in circumference. The lungs were mottled light and dark red and floated in water. Microscopically they showed poor aeration with atelectasis. The alveolar ducts were distended and there was mild subpleural and interstitial emphysema. The alveoli contained many squamae and granular eosinophilic material. The spleen weighed 20 grams and showed superficial lobulation of its lower pole. The red pulp was congested and contained a large number of nucleated red blood cells which exhibited marked anisocytosis. The liver weighed 140 grams and had several small subcapsular hemorrhages. The ductus venosus was patent and had a circumference of 1 cm. When sectioned the hepatic sinusoids were congested and the Kupffer cells contained a large amount of golden granular pigment. There was marked extramedullary hematopoiesis in the liver, as well as in the pancreas, kidney, testes, epididymis, and thymus. The pancreas was normal and microscopically contained normal acini and islet tissue. After careful dissection in the right suprarenal area, only fatty tissue was found. On the left side 2 adrenal glands were present. These each measured 2 by 0.8 by 0.5 cm. and their total weight was 0.53 gram. They had the texture of adrenal tissue but were more oblong in shape than the normal gland. On close inspection many small lobules could just be distinguished on the surface. The cut surface had an inner red zone and an outer tan layer.

Microscopic sections of the tissue from the right suprarenal area showed only fat. Both of the left adrenal glands showed gross disorganization of architecture with increased fibrous tissue interlacing between abnormal lobules and normally arranged cortices (Fig. 1). The separate lobules varied in size from 0.5 to 0.1 mm. in diameter. They had a thin outer rim resembling glomerulosa cells and a central zone resembling zona fasciculata cells arranged in radial cords. The normally arranged cortex was thin with diminution of all 3 layers. The cells in the zona reticularis had deep-staining nuclei and vacuolated cytoplasm. Increased fibrous tissue separated

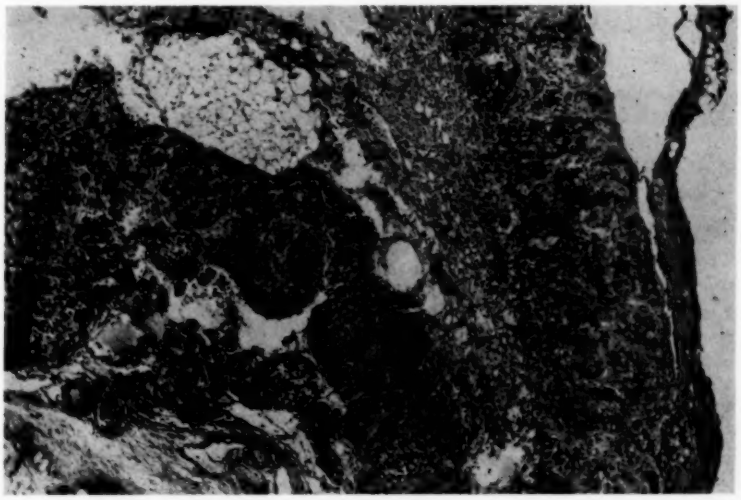

Fig. 1. Section of adrenal gland showing disorganization and nodular formation. (Hematoxylin and eosin. ×125 [approximately]; reduced ⅕.)

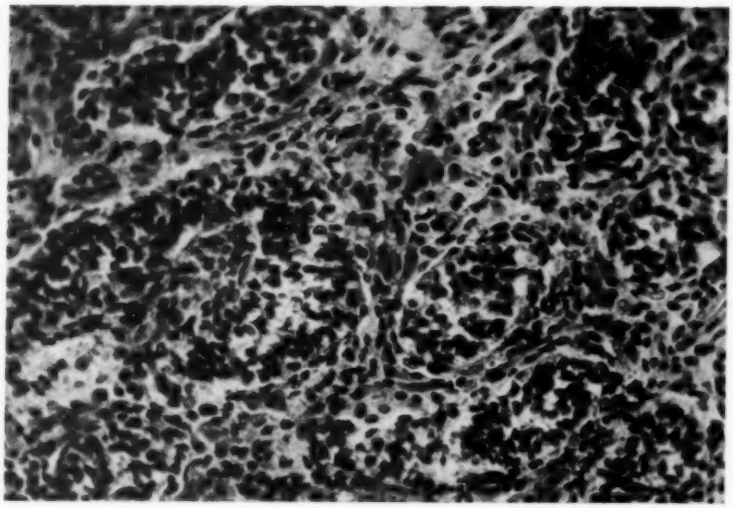

Fig. 2. Section of testes showing interstitial cells with granular cytoplasm and some increase in interstitial fibrous tissue. (Hematoxylin and eosin. ×250 [approximately]; reduced ⅓.)

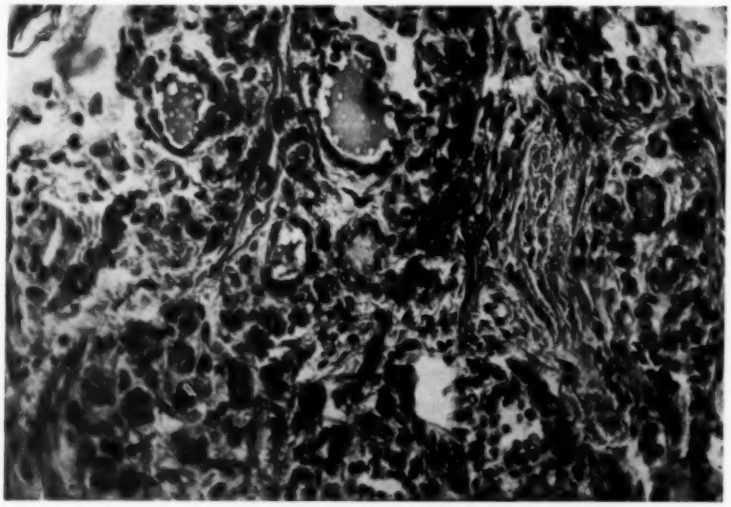

Fig. 3. Section of thyroid gland showing increase in interstitial fibrous tissue. (Hematoxylin and eosin. ×350 [approximately]; reduced ⅓.)

columns of cells in the zona fasciculata. Scattered throughout the 3 layers of cortex, cells resembling glomerulosa cells or fat-depleted cortical cells were seen. In the central portion of the gland there was a thin layer of degenerating fetal cortex with some necrotic cells. The medullary cells appeared normal.

The kidneys each weighed 10 grams and both were normal. The genitourinary tract was developed normally. The testes measured 0.9 by 0.5 by 0.5 cm. and 1.2 by 0.7 by

0.6 cm. They appeared smaller than usual. The tubules were well formed. The interstitial tissue appeared increased in quantity for a full-term, newborn infant (Fig. 2). The thyroid gland weighed only 0.35 gram and was firm in consistency. The follicles were small and separated by an increased amount of interstitial fibrous tissue (Fig. 3).

The thymus weighed 10 grams and was histologically normal. The skull was normally developed. The brain weighed 430 grams, and, except for the pituitary gland, no abnormality was found. At the base of the brain in the position of the normal pituitary stalk, a small nodule was present, completely covered by fibrous tissue and in no way connected with the pituitary fossa (Fig. 4). This nodule when sectioned showed no posterior pituitary cells. The sella turcica was formed normally and covered by a complete fibrous diaphragma sellae through which no pituitary stalk emerged. No anterior pituitary gland was found in the diaphragma sellae, sella turcica, or in serial gross sagittal sections, 5 mm. in thickness, taken from the sella turcica to the posterior pharynx.

DISCUSSION

The findings in this case consisted of absence of the pituitary gland and hypoplasia of the thyroid, testes, and adrenal glands in an infant with jaundice due to A-O incompatibility. The infant died at the age of 19 hours.

The pituitary gland embryologically is formed from union of Rathke's pouch, arising from the primitive pharynx, and the infundibular process from the floor of the diencephalon. Accompanying or preceding this fusion there is resorption of the anterior end of the notochord. The important process for normal development seems to be fusion of Rathke's pouch with the infundibular process.[3, 4]

Various developmental abnormalities of the pituitary gland have been described. Aberrant anterior pituitary tissue has been found within the sphenoid bone in a patent craniopharyngeal canal and in the dorsal wall of the pharynx. Tweedie and Keith[5] described a 6-month-old boy with a median harelip and cleft palate with a cystic swelling in the cleft of the palate which contained pituitary tissue. Melchionna and Moore,[6] by taking serial sections from the sella to the posterior pharynx, were able to demonstrate pituitary gland tissue in the pharyngeal wall in 51 of 54 routine autopsies. Hypoplasia and absence of the pituitary gland in anencephaly and cyclopia have long been recognized.[7-11]

The report by Quirll[12] of a 65-year-old woman with chondrodystrophy and absence of the pituitary gland was not convincing. Grünthal and Keller[13] in 1943 described autopsy findings in a 26-year-old male mentally defective dwarf who during life had shown extreme thirst dating from early infancy. He found hypoplasia of the pituitary gland with generalized hypoplasia of other endocrine organs. The anterior pituitary gland consisted of fat and connective tissue in which only traces of parenchymal tissue were found. The posterior lobe was missing. In the hypothalamus the paraventricular and supraoptic nuclei were represented by only a few damaged nerve cells. The rest of the brain was normal.

Mosier[14] reported pituitary hypoplasia in a twin girl who had signs of adrenal insufficiency and who died at 2 days of age. The adrenal glands closely resembled those in the present case. The pituitary gland weighed 0.053 gram. Survival of an infant with an ectopic and hypoplastic pituitary to 15 months of age has been reported by Ehrlich.[15] The child was dwarfed and the adrenal gland was hypoplastic but normal in shape. The thyroid gland was considered normal.

Independently, Blizzard and Alberts[1] in June, 1956, and Brewer[2] in January, 1957, described infants with absence of the anterior pituitary gland and with features strikingly similar to the present case. The findings in these 3 cases are compared in Table I. From these data it is apparent that the premortem diagnosis of pituitary agenesis or aplasia would be very difficult if not

A *B*

Fig. 4. *A* and *B*, The base of brain showing absence of pituitary stalk and the smooth nodule exposed after the superficial fibrous tissue had been removed.

impossible. One might expect a change in serum sodium and chloride concentrations but in Blizzard and Alberts' case this was not so. The length of life almost precludes endocrine analyses.

Interesting pathologic features are present which may help to elucidate the mechanism of endocrine development. The size of the fetus was not affected and it would appear that the pituitary gland is not essential for growth of the fetus. The posterior pituitary gland in Brewer's[2] case was normal whereas in Blizzard and Alberts'[1] and in the present case no normal posterior pituitary gland was found. The absence of the posterior pituitary gland in 2 cases supports the work of Smith and Dortzbach[16] who showed that in tadpoles cutting the pars buccalis prevented development of the posterior pituitary gland. From Brewer's case, however, it appears that the posterior pituitary lobe can develop independently of the anterior pituitary lobe. In each of these cases it is possible that the pituitary was present in the embryo but later degenerated.

The appearance of the sella turcica covered by a smooth diaphragma sellae with no remnant of a fibrous stalk connecting with the infundibulum may be considered as evidence that the pituitary gland had never developed; however, atrophy of the pituitary gland in early fetal life might also produce this condition. From the evidence put forward by Jost and Danysz[17] in their decapitation experiments in rabbits, the gland is necessary before 20 days of gestation (midpregnancy) for normal male differentiation of external genitals. It has been suggested by Wilkins[18] that the pituitary gland acts by stimulating secretions of the testes which in turn stimulate male secondary sex characteristics or inhibit the inherent tendency to female secondary sex differentiation to promote the normal development of male external genitals. This evidence is surmised from animal experiment. Bruner[19] has shown that chorionic gonadotrophin exists in the human fetus in a concentration which would probably have a physiologic effect. In the absence of a pituitary gland, normal male sex differentiation in the human might result from stimulation of Leydig cells to produce andro-

Table I. Comparison of three cases of absence of the anterior pituitary gland

	Blizzard	*Brewer*	*Present case*
Maturity	40 weeks	34 weeks	40 weeks
Weight	8 pounds	4 pounds	8 pounds
Sex	Male	Female	Male
Clinical course	Cyanosis Apnea Small penis Undescended testes	Cyanosis Apnea Bilateral harelip and cleft palate	Cyanosis Apnea Jaundice A-O incompatibility
Age at death	18 hours	4¾ hours	19 hours

gen by chorionic gonadotrophin or other hormones present during pregnancy. The presence of Leydig cells in this case is striking and, along with normal male external genitals, lends support to such a hypothesis. In Blizzard and Alberts'[1] case there is absence of Leydig cells and they postulate that the pituitary gland may have been present and then degenerated after it had stimulated male sex differentiation.

The abnormal development of the adrenal glands seems to indicate that the pituitary is necessary for their normal development in the fetus. Hypoplasia of the adrenal glands in anencephaly is well recognized[20]; the glands show diminution in size and weight with only traces of fetal cortices. A similar picture is described by Blizzard and Alberts[1] and by Brewer.[2] In Mosier's[14] cases the adrenal gland is similar to this one with lobulation and generalized thinning of adult and fetal cortices. The function of the fetal cortex is not known. The condition of collapse and apnea may have been due to absence of adrenal cortical hormones. The thyroid gland showed marked increase of interstitial fibrous tissue. Although the change was not as striking as that in the adrenal gland, the normal development of the thyroid gland seems to have been altered by absence of the fetal pituitary. It has been shown by Aron[21] that the thyrotrophic hormone does not pass from maternal to fetal circulation. The findings in this case lend support to the concept of the inability of thyrotrophic and adrenocorticotrophic hormones to pass the placental barrier.[2] The islet tissue in the pancreas and the adrenal medulla showed normal development.

SUMMARY

This is the third reported case of absence of the pituitary gland with death in the neonatal period. The clinical course in all 3 cases consisted of cyanosis and apnea with death in the first 19 hours of life. The autopsy showed changes in the thyroid, adrenal, and testes and demonstrated the dependence on the pituitary for development of these glands.

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MEDICAL PROGRESS

The problem of staphylococcal infection in newborn infants

Heinz F. Eichenwald, M.D.,* and Henry R. Shinefield, M.D.**

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STAPHYLOCOCCAL infection and disease have undoubtedly plagued man through the ages. As the mysterious cause of laudable pus, the action of the staphylococcus was looked upon with favor for many decades, but after Pasteur provided the bacteriologic key to the puzzle and Lister's principles of aseptic surgery were adopted universally, the bacterium was assigned its rightful place as a pathogen against which the surgical patient must be protected. While pemphigus of the newborn was first described in 1773, it was not until 1865 that Tilbury Fox pointed out that this disease was contagious.[1] In 1889 the first American nursery epidemic of pemphigus was described,[2] with *Staphylococcus aureus* being identified as the cause in 1891.[3] In a remarkable paper, which probably represents the first epidemiologic study of a nursery outbreak, Call,[4] in 1904, reported on severe staphylococcal infection of infancy which occurred in a hospital where "all babies were kept in a [single] nursery." She commented on the occurrence of associated breast abscesses in mothers and stated "there is absolutely no means of stopping the spread of the infection except by the complete isolation of both mother and child." More than half a century later this same approach is again gaining some favor because of the failure of other methods of control.

It is the purpose of this paper to present a brief discussion of the nature of the staphylococcus and of our present capabilities of dealing with it, and to point out areas for further research. A summary of knowledge of this bacterium is not possible because of limitations of time, personal knowledge, and space; for detailed information the reader is referred to Elek's recent work, *Staphylococcus Pyogenes*.[5]

THE STAPHYLOCOCCUS

According to the most recent revision of Bergey's Manual,[6] staphylococci are now

From the Department of Pediatrics, The New York Hospital-Cornell Medical Center.

Supported by Grants E-944, E-998, and E-2846, of the National Institute of Allergy and Infectious Diseases, National Institutes of Health.

**Markle Scholar in Medical Science. Address, The New York Hospital-Cornell Medical Center, 525 East 68th Street, New York 21, N. Y.*

***Postgraduate Fellow, The National Foundation.*

classified into only two species, *Staphylococcus aureus,* which includes those strains that produce coagulase, and *Staphylococcus epidermis,* whose differential feature is the lack of coagulase production.

The criterion of pigment production to differentiate species has therefore been discarded, and the term *Staphylococcus albus* is no longer used. This change in nomenclature is, no doubt, due to the fact that pigment production, or the lack thereof, is related closely to such environmental factors as temperature, time, carbohydrate source, electrolyte concentration, etc., and the fact that a staphylococcus that appears to lack pigment under some conditions may possess all the known virulence factors and be, in fact, pathogenic. The common practice of considering non–pigment producing staphylococci as contaminants is, therefore, fallacious.

The medium used in most hospitals for staphylococcus isolation (blood agar) is not very suitable for the demonstration of pigment, since many strains which appear white under these conditions show a deep orange color when transferred to more suitable media.

Despite intensive investigations, the mechanism whereby *Staph. aureus,* a normal inhabitant of the skin and nasopharynx, initiates disease remains unknown. Obviously, this is a complex problem involving not only "virulence factors" in the parasite but also changes in the defense mechanism of the host. Although many attempts have been made to correlate the presence of certain "virulence factors" with potential pathogenicity, it is clear that while the activity of many of these factors can be demonstrated in vitro, their relation to in vivo activity is much less clear.

The "virulence factors" most readily determined include alpha hemolysin and coagulase production, but many strains of pathogenic staphylococci also produce dermonecrotoxin, leukocidin, a lethal toxin, and a variety of other hemolysins. Some strains produce an enterotoxin which is responsible for the symptoms of staphylococcal food poisoning, but if this is a more general property shared by many strains, it is unknown because of the technical difficulties encountered in attempting to demonstrate its presence.

The simplest method for assessing the pathogenic potential of a given strain of staphylococci is the coagulase test, which has been carried out by a variety of techniques.[7, 8, 9] The tube method is favored by most investigators. It must be emphasized that 50 per cent of human plasma contains coagulase inhibitors, thus either human material known to be noninhibitory or rabbit plasma should be used.[10]

Production of alpha hemolysin cannot be demonstrated by the use of an agar plate containing human blood since alpha hemolysin is inactive against human erythrocytes, acting only on sheep, bovine, and rabbit cells.[5] The zones of hemolysis seen on plates prepared from human blood (the material generally used in hospital laboratories) is due to a synergistic action of delta hemolysin and proteinase. Under these conditions many coagulase negative staphylococci appear to produce hemolysin.

STAPHYLOCOCCUS TYPING

The only practical method presently available for the differentiation of coagulase positive staphylococci into various subtypes involves the use of phages,[11] although techniques for antigenic analysis have been achieved recently.[12] Most coagulase positive staphylococci isolated from hospital sources can now be categorized by typing.

The application of phage typing methods to epidemiologic problems has served to clarify many of the unknowns in staphylococcal epidemics. The detailed identification of phage types which this technique permits makes it possible to determine the source and routes of transmission of staphylococcal cross-infection, food poisoning, wound infections, etc. Using these typing procedures, Shaffer and colleagues[13] have shown clearly that the predominant producer of nursery epidemics of staphylococcal disease is a *Staph. aureus* which has the

phage pattern 42B/47C/44A/52/80/81. Other types incriminated, but much less frequently so, are types 52, 52A, and 52/79.

Antibiotic sensitivity patterns ("antibiotograms") may be used on a limited scale to label strains encountered in certain simple epidemiologic problems. Primarily, however, this technique, available in even the smallest laboratories, can be used for preliminary screening for identity and for selecting those strains which need further study by phage typing. For example, if a staphylococcus showing a particular antibiotogram is isolated from several infants with staphylococcal disease and an organism with a similar pattern is found in the nasopharynx of one of the attendants, one is justified in the preliminary conclusion that these organisms are identical and phage typing of the respective staphylococci is then used for confirmation.

THE NATURE OF THE PROBLEM

Staphylococci as agents of disease have suffered two crushing defeats in the last century, the introduction of aseptic surgical technique and the discovery of antimicrobial agents. These two separate and distinct improvements in medical care, however, have failed to relieve man of this scourge. Why have we failed while we were simultaneously successful in eradicating many of the major parasites of modern mankind? The answer to this question appears to rest in a difference in host-parasite relationship. Those diseases that have been banished successfully are caused, generally, by highly virulent organisms—organisms which regularly produce illness in low infective doses. The presence of this type of parasite is apparent to all concerned, since the host will show an obvious and usually well-defined illness. Thus, and perhaps paradoxically, the most virulent microbes, those that regularly produce disease, were the first to disappear. These organisms, in the long run, are relatively unsuccessful parasites since the host, by various external means, eliminates them.

The most successful parasites in nature are those that are able to establish a symbiotic existence without necessarily producing obvious discomfort to the host. The latter, therefore, will make no attempt to eradicate the parasite nor will society restrict the individual's activity in order to prevent dissemination of infection. The parasite is free to spread throughout the population and to become increasingly inaccessible to direct attack because of its wide and universal distribution. Occasionally, disease may be produced because of a temporary disturbance in the balance between host and parasite, but even if action then is taken belatedly to eradicate the offending organism in the sick patient, the ultimate survival of the parasite in nature has already been assured by its widespread dissemination.

The staphylococcus represents an excellent example of the successful parasite. Its presence is nearly universal; it is one of the few organisms capable of prolonged survival in the nasopharynx of the newborn infant, child, or adult. Furthermore, it possesses the ability to adapt itself rapidly to noxious situations, such as exposure to antimicrobial agents. The same coagulase positive staphylococcus so harmlessly colonizing the nose can cause sepsis: all or most organisms of this type are capable of producing wound infection and pyoderma.

Medical bacteriology has always concerned itself with the parasite, not with the host. Yet, on final analysis, factors of the host determine whether this "harmless" staphylococcus in a given patient will cause disease. As McDermott has pointed out,[14] our present difficulties "stem from the fact that we are almost wholly ignorant of the mechanism of staphylococcal infection and disease."

From the clinical standpoint, the problem of virulence of a given staphylococcus is difficult to assess, partly because the word itself has no clearly defined meaning. From studies performed in human volunteers, there is no evidence that the epidemic strains of staphylococci such as Type 80/81 possess a significantly greater ability to cause lesions on subcutaneous inoculation than do other strains.[5] Yet epidemiologic ob-

servations clearly indicate that in newborn infants one phage type of staphylococci, Type 80/81, has far greater disease-causing ability than do other coagulase positive, typable staphylococci. For example, of 100 newborn infants colonized with staphylococcus Type 80/81 and followed closely by us, 48 developed signs and symptoms of staphylococcal disease within 6 months after discharge. This high rate of illness may be compared to the relatively low rate of 5 per cent found among a group of "control" infants discharged from the same hospital harboring other phage types of coagulase positive staphylococci.

On the other hand, the existence of special strains causing wound infections in surgical patients is doubtful; wound sepsis appears to be no more common with Type 80/81 than with other coagulase positive staphylococci.

These observations are not mutually contradictory, though they might appear to be at first glance. The introduction of a staphylococcus into a wound or inoculation into the skin in human volunteers represents, as far as the parasite is concerned, quite unusual situations. In both of these circumstances, the factors of invasiveness have been eliminated because at the moment infection is established the organism is already within tissue.

In newborn infants, on the other hand, the ability of the bacterium to cause disease is determined, at least partially, by a series of other factors acting before invasion has occurred. The ability of the organism to disseminate and to persist in a host, its rate of multiplication, and its ability to withstand the pressure of other parasites all help to determine whether infection can continue for a sufficient time to permit overt disease to occur whenever host defenses are weak or whether the parasite will be eliminated before this can take place.

THE INFANT AS A RESERVOIR OF STAPHYLOCOCCAL INFECTION

It is well established that the infant is an important reservoir of staphylococcal infection, often the primary one in a nursery situation. The importance of the infant in this regard is particularly pronounced when a large number of babies are together in one nursery. The introduction of a single infected infant, particularly if he should be a "cloud baby,"[15] may, under suitable conditions, result in infection of most of his roommates. Because newly born infants, highly susceptible to colonization, are continuously admitted to such a unit, a never-ending chain of infection is set up in which the older infants infect the younger ones.

In those epidemics where infant-to-infant transmission of the staphylococcus is found, three sources of spread have been incriminated: (1) the nose[13] (or nasopharynx), (2) the skin,[16] and (3) the umbilical stump.[17]

There is little doubt that the respiratory tract of infants may act as an important source of microorganisms, particularly if a concomitant virus infection is present. The virus acts to increase greatly the amount of staphylococcal dissemination, producing the so-called "cloud baby."[15]

Dissemination from the skin has also been demonstrated to occur in some epidemics, and British investigators particularly have emphasized the importance of the cord stump as a possible source of microorganisms.

In any particular infant-to-infant epidemic one or several of these sites may act as the predominant source of staphylococci. Which site assumes this role appears to be determined to a large extent by the particular strain of staphylococcus involved. We have observed marked differences in the ability of various strains of staphylococcus phage Type 80/81 to colonize these areas. Some strains are excellent colonizers of the respiratory tract; others prefer the skin and do poorly in the nose or umbilical stump, while another may propagate most readily in the cord. These differences in affinity in respect to site of multiplication explain why control measures aimed in a single direction may appear successful in one outbreak but unsuccessful in another. Procedures

with such limitations include painting cord stumps with antiseptic dyes, washing babies with hexachlorophene-containing lotions, and applying antibiotic ointments topically to the nose of infants.

Under some conditions the role of the nursery staff in the dissemination of staphylococci may be quite passive. The personnel's continued exposure to the heavily contaminated environment of the nursery may result in some of them becoming carriers and these individuals may then spread the offending organisms to other parts of the hospital, but their role in maintaining the course of the epidemic in the face of significant aerial contamination may be quite minor.

This should not be interpreted as an attempt to minimize the role of carriers in the epidemiology of staphylococcal infection. They are of obvious importance in starting the chain of infection. It has been demonstrated clearly that the infant is far more likely to harbor the strain of staphylococcus common among his attendants than those of his mother,[16] and that in those circumstances where massive aerial contamination by the infants is not possible, the attendants represent the most important factor in the dissemination of particular types of staphylococci.[15]

It is Shaffer, Baldwin, and Wheeler's[18] belief that there are marked personal differences between adult carriers in their ability to disseminate any given strains of staphylococci. Individuals with overt staphylococcal lesions or disease are generally highly infectious to infants, but, in our experience, asymptomatic carriers may sometimes be equally infected. Unfortunately, there are no generally applicable methods to distinguish those carriers with a high degree of infectiousness from those with minimal infectiousness. The difference of one individual compared to another does not appear to be related to obvious differences in nursing technique, personal habits, hygiene, or frequency of hand washing. Furthermore, some adults appear to acquire nasal colonization more readily than others. It would appear that the spectrum of susceptibility among adult groups to nasal colonization with a given strain of staphylococcus probably covers the range from almost total resistance to moderate susceptibility. Not only are host factors of importance in determining whether colonization will occur in any given individual, but there are also marked differences between various strains of staphylococci. Even in infants, many strains are very poor colonizers, and, should they succeed in multiplying in the baby's nasopharynx, they will often disappear again relatively rapidly. On the other hand, other strains, particularly those belonging to the 80/81 phage type, possess a very high colonizing efficiency. Colonization results from exposure to a small number of bacteria and once infection has been established, the organism persists for very long periods of time.

There may be competition between various strains of staphylococci as well as between staphylococci and other bacteria in their attempt to colonize a nasopharynx. In general, a more efficient colonizer eventually seems to replace a less well-adapted one; however, once one strain of staphylococcus is established in the nasopharynx, it appears to be more difficult for this patient to become colonized by other strains. A consideration of these factors leads to two interesting conclusions, neither one of which has as yet been confirmed experimentally. (1) By maintaining an infant in a highly sterile, individual environment, as provided by small, well-ventilated nursery units, he may be rendered more susceptible to colonization from carriers and may become colonized with staphylococcus Type 80/81 after a relatively transient exposure. The extent to which a carrier is infectious may, therefore, depend to some degree on the nursery environment of the infant under his care. (2) Colonization with other less virulent staphylococci shortly after birth may present the individual infant's most active defense mechanism against more pathogenic strains.

It should be pointed out that the prop-

erties of colonization efficiency and of virulence are not necessarily interrelated. We have encountered phage types equal to staphylococcus Type 80/81 in ability to spread among infant population groups with, however, a greatly diminished ability to produce overt disease. The special problem presented by phage Type 80/81 exists because many strains of this particular type possess not only high colonizing ability but also a greater potential for causing clinical disease than other staphylococci generally encountered.

Whether fomites can act as sources of infection in newborn infants is a matter of considerable importance. During outbreaks of staphylococcal infection, these bacteria can be cultured readily from dust, linen, and any other object exposed to air. The cultural demonstration of the organism in the environment does not necessarily imply that infants can become infected from these fomites; so far, no clear-cut study has been performed to indicate that fomites are a source of staphylococcal infection. Our present data indicate that environmental contamination may, in fact, play a negligible role in this regard. Perhaps staphylococci coated with dust and dirt or adsorbed on large particles lose much of their infectivity while still remaining viable. It should be pointed out, however, that good evidence exists that fomites play a role in surgical wound infection.

CONSTRUCTION AND MAINTENANCE OF A NURSERY

From the discussion presented in the preceding paragraphs, it would appear possible to arrive at some logical deduction concerning those features of a modern nursery unit which would promote the greatest safety for both infants and staff, as far as cross-infection is concerned.

Since infant-to-infant spread of infection may occur, steps should be taken to minimize this possibility.

1. The number of infants sharing a common air supply should be small, obviously the smaller the better. Four to 6 infants in a unit would appear to represent a good compromise between such factors as economy of space, nursing time, ease of observation, and safety.

2. The infants should be separated widely within the unit; a space of 30 square feet per infant probably represents the minimum as long as there are only 4 babies per unit. It would appear from our observations that the greater the number of infants in a given space, the more square feet per infant are necessary to protect them from each other.

3. A ventilating system should be provided which is capable of supplying at least 12 to 15 draft-free changes of clean air per hour. This system should also produce a slight positive pressure within the nursery so that contaminated material from public corridors, mothers' rooms, etc., does not blow into the unit when the doors are opened.

4. In hospitals with obstetrical services of sufficient size, a cohort or rotation system of admission and discharge of infants should be provided. All infants born within a single fixed time period (usually 24 hours) are admitted to Unit 1. These infants represent the "cohort." All infants born in the next time period are admitted to Unit 2, the following group to Unit 3, etc. When the infants in Unit 1 are ready for discharge, they are sent home as a group. The unit is cleaned, restocked with fresh linen and other supplies, and a new cohort admitted. Any infant that remains in the hospital longer than other members of his group is transferred to an "overflow" nursery (usually the isolation or observation unit). With this system, a continuous direct chain of infection from infant-to-infant cannot occur; each cohort has no contact with any other cohort.

These measures will minimize the chance of successful infant-to-infant transmission of infection. The problem of attendant carriers is, of course, quite different and must be approached separately.

1. The infants should have contact with the smallest number of attendants needed

for adequate nursing care. Nursing assignments should be arranged in such a manner that the same nurse cares for the same infants throughout their stay in the nursery. Obviously, the more attendants are available, the fewer infants each would have contact with, and an attendant who is a carrier of a pathogenic staphylococcus will succeed in infecting the smallest possible number of infants.

2. All personnel who have direct contact with infants should have cultures taken at frequent intervals in order to detect carriers of phage types of staphylococci known to be pathogenic. With the present availability of commercial preparations of all important staphylococcal phages, many hospitals will find it possible to do this screening procedure in their own laboratories; otherwise, public agencies must undertake this task.

3. Any attendant with suspected staphylococcal disease must be excluded rigidly from contact with the infant. Similarly, in the presence of any type of respiratory infection, the individual must be excluded from the nursery. It is obvious that personnel should not be penalized financially for voluntary reporting of illness.

In order to obtain reliable data about the success of these methods in reducing the incidence of nosocomial infection with staphylococci and other organisms, it is desirable to have in operation at all times some systematic device for follow-up of infants discharged from the nursery. This would give an indication of any untoward incidence of some particular type of disease occurring after discharge. Various methods of follow-up are available; the least expensive and most convenient one is the telephone survey.

THERAPY OF STAPHYLOCOCCAL DISEASE AND INFECTION

Some of the special characteristics of staphylococcal disease are of importance in formulating a rational therapeutic approach to a patient.

1. Whenever staphylococci succeed in invading the deeper tissues of the host, formation of an abscess is the rule. Once these local foci have formed, the staphylococci within these lesions virtually are impossible to eradicate even with optimal antimicrobial therapy.

2. Even under the best conditions, staphylococci are killed in vivo exceedingly slowly by available agents. Relapse rates are therefore high, and the illness tends to run a chronic course with remissions and exacerbations.

3. Staphylococci on mucous membranes of the nose and nasopharynx and within respiratory passages cannot be eliminated regularly by any known method.

4. The capacity of strains of staphylococci to become resistant to chemotherapeutic agents is high.

5. Staphylococcal infections acquired in the hospital represent an entirely different problem from the same infection acquired in the community.

Consideration of these factors suggests several logical approaches to the therapy of the individual patient.

1. Abscesses or any localized accumulations of pus, as found in boils, empyema, and osteomyelitis, etc., should be incised as soon as possible and adequate and continuous drainage established.

2. Chemotherapy must be continued for a sufficiently long period of time to permit the host to wall off and otherwise control the parasite. In infants with staphylococcal pneumonia or osteomyelitis, 4 or 5 weeks of therapy should be considered the minimum.

3. The treatment of asymptomatic carriers of staphylococci with systemic or local therapy in an attempt to eradicate the microorganisms cannot be shown to produce an increased rate of cure over that one would achieve by using no therapy at all.

4. The initial medication selected should depend on the clinical setting in which the specific illness occurs. An acute staphylococcal illness arising outside the hospital in an individual without recent direct or indirect contact with such an institution is still often caused by an organism found to

be sensitive to penicillin and to the tetracyclines. Whenever the bacterium is susceptible to penicillin, this agent is the drug of choice when given intramuscularly and in adequate doses.

Many physicians routinely use a second antimicrobial agent in treating penicillin-sensitive staphylococcal infection, although the value of such combined therapy is doubtful either from the standpoint of achieving a better therapeutic response or of preventing the emergence of resistant strains. Staphylococcal disease arising within a hospital or in adults in close contact with young infants must be assumed to be due to relatively resistant strains of the organism and the chemotherapeutic agents employed should be selected accordingly: erythromycin and novobiocin are probably the generally most useful drugs. It is the authors' impression that the therapeutic value of chloramphenicol in the treatment of severe staphylococcal disease in children has been overestimated.

In patients severly ill with their disease or in individuals whose response might be deficient, such as children receiving radiation therapy, antileukemia drugs, steroids, newborn infants, etc., the most effective therapy at hand should be employed. In infancy and early childhood the most potent agent available at present is bacitracin administered intramuscularly in a dosage of 500 units per kilogram every 12 hours for 1 week to 10 days, followed by an appropriately extended course of another drug such as novobiocin, erythromycin, etc. In this newborn age group, the only observable toxic effect of bacitracin is renal irritation, as shown by transient or reversible albuminuria and rarely microscopic hematuria. The urine rapidly reverts to normal upon discontinuation of therapy and it is our policy not to stop administration of bacitracin despite the appearance of these findings. Vancomycin, ristocetin, and kanamycin, in our experience, are not only less effective when used in infants but are accompanied by a significantly greater incidence of undesirable and occasionally serious side effects. It seems appropriate, in this connection, to emphasize the fact that an agent which shows a significant proportion of toxic manifestations in adults may prove relatively safe in newborn infants (bacitracin), while a drug relatively innocuous in an adult may prove toxic in infants (chloramphenicol). Furthermore, infants and adults differ in their response to infection. Since the efficacy of an antimicrobial agent depends, at least to some extent, on host factors, it is not surprising that an agent which may appear efficacious in the adult may perform poorly in an infant and vice versa.

ANTIBIOTIC SUSCEPTIBILITY TESTS

It is of utmost importance to obtain information as rapidly as possible regarding the antibiotic susceptibility of the staphylococcus causing disease in a particular patient. The agar-diffusion method (disk) is widely employed and is generally satisfactory for most antibiotics tested except for penicillin and chloramphenicol. In the case of penicillin, the only drug where serum levels in the patient can be varied readily between 1 unit and 100 units or more by increasing the dose, it is of importance to obtain precise quantitative information about susceptibility because of the high relative efficacy of this agent. The tube dilution method of testing is therefore desirable. With chloramphenicol, we have found only little correlation between staphylococcal susceptibility, as shown by the agar diffusion method, and the clinical response achieved.

The disk method is satisfactory only, of course, if properly performed and interpreted. The zones of inhibition produced with various antibiotics will vary in size, and although it is tempting to relate relative size of the zone to the degree of susceptibility or resistance, this cannot be done. Antibiotics vary in their rate of diffusion in agar and the diffusion rate obviously is not related to therapeutic efficiency. Thus, size of the zone is more a measure of diffusibility than of susceptibility and depends also on

the culture medium used, the thickness and wetness of the agar, and the density of the inoculum. Thus if only a disk of one concentration is employed for each antibiotic, the size of the zone must be disregarded and only its presence or absence be taken into account. The results can be recorded as resistant or susceptible and the efficacy of the various agents cannot be compared. If two or more suitable concentrations for each antibiotic are used, the results may be reported as sensitive, moderately sensitive, or resistant.

CHEMOPROPHYLAXIS OF STAPHYLOCOCCAL DISEASE

The success that antimicrobial agents have achieved in the treatment of certain specific infectious conditions has led to their increasing use for the prevention of infection in general. Since there appears to be an increasing tendency to depend on chemoprophylaxis for protection against staphylococcal infection, a brief discussion of available information about such use among infant populations is indicated.

Generally the prophylactic use of antibiotics is considered in two situations: (1) during periods of high staphylococcal infection incidence in a nursery to reduce overall colonization rates and (2) to protect an individual infant known to be a carrier of a potentially pathogenic staphylococcal phage type against extension of his infection during periods of increased risk, such as during viral upper respiratory infections or during an operation with or without general anesthesia.

Actually, only the first of these uses has a well-established foundation. Shaffer and his associates[19] have reported successful use of erythromycin to terminate epidemics with susceptible strains of staphylococcus Type 80/81, and we have used erythromycin and novobiocin with similar success. Experience with these drugs has led us to formulate several general principles concerning their use. Obviously an antimicrobial agent should be selected which is known to be effective against the particular strain of microorganism one wants to suppress. The drug must possess a sufficiently low level of toxicity to make it acceptable as a prophylactic tool. Since it is seemingly impossible to eradicate a staphylococcus once colonization has become established, chemoprophylaxis in nurseries will be of benefit only to infants who have not become infected prior to its use. It is of no benefit to individuals already colonized. Therefore the first dose of drug must be administered to an infant as soon after birth as possible, certainly within an hour or less after his arrival in the nursery. Succeeding doses should be given at least every 6 to 8 hours as long as the infant remains exposed to the infected environment. Therapeutic dosage should be used for prophylaxis. The temptation to use small amounts of drug should be resisted.[18]

Chemoprophylaxis can only be considered an emergency measure to be used "to buy time" so that an infected carrier, a "cloud baby," or a break in technique may be identified and the situation corrected. Prophylaxis is not a means in itself and its indiscriminate use in newborn infants is inexcusable. Widespread and ill-advised use of these chemotherapeutic agents will only result in the selection of increasingly resistant strains of bacteria, both in individual patients and in groups. In the New York area almost every strain of staphylococcus Type 80/81 is already highly resistant to erythromycin and during the fall of 1959 strains resistant to novobiocin have appeared with increasing frequency. Furthermore, it must be considered that we know little of the long-term toxicity of many chemotherapeutic agents when used in newborn infants.

SUMMARY

The problem presented by *Staphylococcus aureus* to newborn infants is not a new one, but in recent years the emergence of strains of the organism uniquely adapted for survival in this group has greatly increased our difficulties in dealing with the parasite.

A rational approach to the problem de-

mands knowledge of the pathogenic, ecologic, and epidemiologic properties of the bacterium. It is probable that our present knowledge is sufficiently advanced that its proper and conscientious application can lead to a great reduction in staphylococcal infection and disease among newborn infants.

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TROPICAL PEDIATRICS

Treatment of kwashiorkor with moderate amounts of protein

Reginald F. A. Dean, M.R.C.P., Ph.D.

KAMPALA, UGANDA, EAST AFRICA

FOR several years a large part of the resources of the Infantile Malnutrition Research Unit has been employed in attempts to produce cheap but satisfactory foods that might help to prevent the occurrence of malnutrition in Uganda. For obvious reasons, ingredients locally available have been used, and, as a dry material has great advantages in an equatorial climate, the ingredients have been made into a biscuit, which has been hammer-milled into a fine powder. The ingredients are whole peanuts (used for their protein and calories), corn flour (used chiefly for its calories), wheat flour (used for the binding qualities of its gluten), sugar (used chiefly for its sweetness), cottonseed oil (used for its calories and for its preservative powers) and dried skim milk (used chiefly for its amino acids and its minerals).

From the Medical Research Council, Infantile Malnutrition Research Unit, Mulago Hospital, Kampala, Uganda, East Africa.

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**Address: Mulago Hospital, P.O. Box 2072, Kampala, Uganda, East Africa.*

The methods of preparation are given elsewhere in an account of the balance experiments that were used to provide rapidly the means of deciding the optimum amount of the dried milk that should be included and how it should be included. The experiments showed that good nitrogen retention could be obtained with 15 per cent of the milk and that it should not be cooked with the other ingredients of the biscuit, but added after the biscuit had been powdered.[1]

The consideration of many factors, such as cost, acceptability, and the presumed need for abundant calories as well as protein, led us to fix the percentage of protein in the finished material at about 20 and the ratio of protein calories to total calories at about 1:6. Our experimental plan was based on the use of the biscuit for the treatment of children who had been admitted to the wards of the Unit for the treatment of kwashiorkor and on comparisons of the biscuit with a diet providing an equivalent amount of protein, all from cow's milk. We found that most of the children would take each day only 150 to 200 Gm. of the biscuit and we realized that they would therefore be

limited to 30 to 40 Gm. of protein—4 to 5 Gm. per kilogram of body weight. We had previously used larger amounts of protein, but some preliminary experiments showed that the smaller amounts would give excellent results.

The present paper is primarily, therefore, a report on the use of diets that contained moderate amounts of protein. It has been complicated, for reasons that appear later, by the need to divide the cases and results obtained according to the severity of the condition of kwashiorkor found on admission.

MATERIAL AND METHODS

Children investigated. The three diets were used from January, 1958, to June, 1959, and during that time a total of 234 children were admitted to the wards of the Unit. To simplify analysis and to provide groups that might reasonably be compared, the records of 131 of the children 12 to 36 months old were selected for the present purpose. They were children who were undoubtedly suffering from kwashiorkor, who had no proved complication such as dysentery, pneumonia, tuberculosis, severe anemia (of less than 5 Gm. hemoglobin per 100 ml. blood) or any congenital defect, and who not merely survived, but were discharged from the hospital in an improved general condition. The length of stay was usually 3 to 4 weeks.

The children were of various tribes found in the Kampala district, but about half were Ganda and of the rest the large majority were Bunyuruanda or Banyaundi—immigrants to Uganda from the Ruanda-Urundi. No effect of tribe could be discovered, and the tribes will not be mentioned again. Some of the children were brought in from the Unit's country Child Welfare Clinic, some were sent by local medical practitioners or by medical assistants in charge of Government dispensaries, and some had attended the outpatient department of the main Government hospital at Mulago, Kampala. (A few came on the recommendation of parents whose own children had been successfully treated at the Unit.)

Medical and dietary procedures. Nearly every case of kwashiorkor has two main causes. One is a deficient diet. The other is an infection or anything else capable of causing a stay or restriction of protein anabolism. It is this latter factor that produces the overt condition. When the children were admitted, clear signs of infection were not usually found, but penicillin and streptomycin were always given by injection for the first 5 days, or until it seemed likely that they could safely be stopped. If malarial parasites were discovered in the blood, appropriate treatment was given; prophylactic antimalarials were administered regularly throughout each child's stay in the hospital. Hookworms were very seldom present in the stools in such large numbers that treatment was thought to be necessary; treatment was never given until the child had been in the hospital for at least 10 days, and neither the presence of the worms nor their removal could have had an appreciable effect on the results.

The skin lesions that were due to kwashiorkor were left uncovered and had no local treatment of any kind. Some children had angular stomatitis, cheilosis, a fiery red tongue and other signs usually attributed to vitamin deficiences, but no vitamins were used in treatment.

The anorexia, that is the most serious difficulty in the nursing of kwashiorkor could usually be overcome by patience and persistence, but in the last year gavage has sometimes been used. If oral feeding was possible only at the expense of exhaustion or much upset to the child, a fine polyethylene tube, 1 mm. in internal diameter, was passed through the nose into the stomach, and the food was given down it by syringe or continuous drip. In the first days after admission, the food was given at 3 hour intervals to the most seriously ill children, but the advantage of feeding was always weighed against the disadvantages of disturbed rest, and often, especially at night, a continuous drip was thought to be preferable to waking the child for an oral feeding.

The condition of the children on admission. Every child was examined within a

Table I. Chief signs of severe, moderate, and slight kwashiorkor

Sign	Grading of kwashiorkor		
	Severe	*Moderate*	*Slight*
Weight for age	Low, variable	Low, variable	Low, variable
Muscle wasting	Obvious	Obvious	Not obvious
Subcutaneous fat	Usually well retained	Well retained	Well retained
Hair	Pale, sparse, and easily pulled out	Pale, sparse	Usually discolored
Facial pallor	Marked	Slight	Usually absent
Skin	Typical advanced lesions	Pigmented spots, slight desquamation	Slight cracking
Edema	Usually gross	Moderate	Slight
Misery	Usually extreme	Moderate	Not marked
Interest	Usually poor	Fairly good	Retained
Other signs	Angular stomatitis, cheilosis		

Table II. Percentage of standard weight for age of 445 children admitted for treatment of severe, moderate, and slight kwashiorkor

Grading of kwashiorkor	Percentage of standard weight				Total No.
	90 or more	*89 to 77*	*76 to 60*	*Under 60*	
Severe	9 (5.3%)	43 (25.4%)	73 (43.2%)	44 (26.1%)	169 (100%)
Moderate	9 (6.3%)	25 (17.5%)	80 (55.9%)	29 (20.3%)	143 (100%)
Slight	3 (2.2%)	32 (24.1%)	67 (50.4%)	31 (23.3%)	133 (100%)

very short time—usually less than an hour—after admission to the wards of the Unit, and the results were written on a special form. The grading into "serious," "moderate," and "slight" kwashiorkor was decided at the examination and was very seldom revised. The few exceptions were all of one kind: children in whom the seriousness of the condition had been underestimated. For such children the correction was usually made within a few days. The records of all patients admitted since 1954 were surveyed by another clinician and myself preliminary to the preparation of this report, and it is believed that a single standard has been applied with the minimum of deviation.

The grading was essentially clinical, and a correlation with the more objective findings was, therefore, of particular interest.

The basis of the grading is set out in Table I, but anyone who has had experience in the difficulties of diagnosis of malnutrition will realize that the definitions for such a purpose cannot be absolute. The most surprising item is probably weight for age, which was the same for "severe," "moderate," and "slight" cases. In Mexico, Gómez and his collaborators[2] were able to use weight for age as an index of severity, but it cannot, apparently, be used in Uganda for cases of kwashiorkor. The percentage weight for age was the same, 67, for all three grades. The weight standard used was a local one, obtained from healthy Ganda children attending the Unit's Child Welfare Clinic, and Table II shows the percentage of the standard weight for age of all children admitted to our wards with the diagnosis of "severe," "moderate," or "slight" kwashiorkor from 1954 to 1959. The divisions of 89 to 77 per cent, 76 to 60 per cent, and under 60 per cent of the standard correspond

Table III. Mean values for analysis of serum taken from children on admission

Grading of kwashiorkor	*Total protein*			*Cholesterol*			*Amylase*			*Cholinesterase*		
	No.	*Gm. /100 ml.*	*S.D.*	*No.*	*Mg. /100 ml.*	*S.D.*	*No.*	*Units /100 ml.*	*S.D.*	*No.*	*Units /ml.*	*S.D.*
Severe	40	3.88	0.76	40	113	39	37	58	24	19	58	43
Moderate	39	4.53	0.78	39	110	29	34	72	39	24	59	54
Slight	52	5.42	0.95	52	115	34	44	93	40	28	97	70
Test of difference of means												
Severe—moderate	t = 3.71 (significant)			t = 0.55 (not significant)			t = 1.80 (not significant)			t = 0.45 (not significant)		
Moderate—slight	t = 4.65 (significant)			t = 0.69 (not significant)			t = 4.94 (significant)			t = 3.91 (significant)		

Table IV. Mean values for fractionation of proteins of serum taken from children on admission

Grading of kwashiorkor	*Albumin*			*Globulins*							
				Alpha$_1$		*Alpha$_2$*		*Beta*		*Gamma*	
	No.	*Gm. /100 ml.*	*S.D.*	*Gm. /100 ml.*	*S.D.*	*Gm. /100 ml.*	*S.D.*	*Gm. /100 ml.*	*S.D.*	*Gm. /100 ml.*	*S.D.*
Severe	24	1.50	0.40	0.27	0.12	0.51	0.25	0.48	0.15	1.25	0.44
Moderate	23	1.80	0.54	0.27	0.11	0.50	0.18	0.46	0.15	1.43	0.32
Slight	16	2.24	0.77	0.31	0.11	0.50	0.18	0.56	0.22	1.58	0.18
Test of difference of means*											
Severe—moderate	t = 2.55 (significant)										
Moderate—slight	t = 2.22 (significant)										

*No difference in the means of any of the globulin fractions is significant at the level of P = 0.05, but the value of t for "severe-slight" gamma globulin is 1.96 which is significant for P = 0.07.

to Gómez's classification into Grade I, Grade II, and Grade III malnutrition, and it is clear that weight was not closely related to the clinical judgment of the severity of our cases.

The mean results of the analyses of the serum taken on admission from the 131 children are given in Tables III and IV. We intend to make, at some time in the future, a complete statistical analysis of the findings of all the patients admitted to our wards, in relation not only to the severity of kwashiorkor, but also to the presence of complications and the course of treatment. The mean values in Table III suggest that in the 131 children the results for the estimation of total protein, amylase, and possibly cholinesterase bore some relation to severity, but that those for total cholesterol did not. The fractionations of serum proteins (Table IV) showed that the three grades of severity were associated with different levels of albumin. The gamma globulins exhibited an interesting trend toward increase with the lessening of severity; the difference between "severe" and "slight" cases just failed to reach significance at the chosen degree of probability (P = 0.05), but the trend was probably real.

Because the proportions of "severe," "moderate," and "slight" cases varied in the dietary groups, the mean findings for the serum of the groups has been given in Table V. For various reasons, the chief of which

Table V. Mean values in serum on admission of children in the three dietary groups

Diet	*Total protein*		*Cholesterol*		*Amylase*		*Cholinesterase*	
	No.	*Gm./100 ml.*	*No.*	*Mg./100 ml.*	*No.*	*Units/100 ml.*	*No.*	*Units/ml.*
Milk	60	4.3	60	112	60	66	21	58
Biscuit 15U	35	4.9	35	115	34	91	34	71
Biscuit 8C	36	4.9	36	116	22	86	16	81

was shortage of staff, it was not possible to estimate all four serum constituents in every child, but the results are not invalidated by their lack of completeness.

There was no significant difference in the weight for age of the patients with "severe," "moderate," or "slight" cases in the three dietary groups.

Diets. The milk diet was a mixture of calcium caseinate,* dried skim milk, cane sugar, and cottonseed oil, made up to volume with water. It was suitably low in lactose.[3] The cottonseed oil, which was introduced into the Unit's therapeutic diets in 1955,[4, 5] causes neither vomiting nor diarrhea, even in acutely ill children.

Two biscuit diets were given in competition with the milk diet. One, known as Biscuit 8C, had 8 per cent of dried skim milk cooked with the other ingredients; the other, known as Biscuit 15U, had 15 per cent of the milk, which was added uncooked to the powdered biscuit. The simultaneous alteration of two variables was not entirely satisfactory, but it was made necessary by the length of time—approximately a year—that is needed to complete the trial of a new diet.

Details of the three diets are given in Table VI. The milk diet was a thin fluid, and the biscuit diets were fairly thin gruels made by whisking the powdered biscuit with three or four times its weight of water in an electric mixer.

Some children had the same diet throughout their stay in the hospital. Others had first one diet, then another, but when the diet was altered the total daily protein intake was kept unchanged. The diets were altered for two reasons: in a few children because progress on a biscuit diet was unsatisfactory and it was thought advisable to change to the milk diet, but in most children because we wanted to see the effect of alteration. The use of a child as his own "control" in this way is a procedure that has obvious advantages.

The amounts of the milk and biscuit diets were not calculated strictly according to weight, but were intended to supply protein in the range of 4 to 5 Gm. per kilogram of body weight per day and, therefore, about 120 calories per kilogram. The amounts were not usually altered as the child improved and his appetite increased. All the children were offered sweet banana *(Musa paradisaica)* or cooked banana *(plantains: Musa balbisiana)*, but very few took each day more than 200 Gm. of the bananas, which added only about 2.0 Gm. protein and 200 calories. The children were always under observation, and no other foods were eaten.

The tube feeding that has been described and which can be used to ensure a regular daily intake in spite of anorexia, was not introduced until the last months of the experiments, and many children, therefore, had a smaller intake in the first week of treatment than they had in subsequent weeks. The biscuit diets could not be given by drip, although they could be given with some difficulty by syringe down a polyethylene tube, 2 mm. in diameter. Sometimes they caused vomiting, and children who were very ill were therefore not fed on biscuit as a routine; a failure to achieve an adequate intake might have been disastrous. We realize that our results would have been more acceptable to statisticians if we had treated alternate children with milk and biscuit

*Casilan, manufactured by Glaxo, Ltd.

Table VI. Values for amounts of ingredients of milk and biscuit diets providing 20 Gm. of protein

	Milk diet	*Biscuit 15U*	*Biscuit 8C*
Casilan (Gm.)	15.5	–	–
Dried skim milk (Gm.)	19.0	15.0	8.0
Sugar (Gm.)	15.5	12.0	12.0
Cottonseed oil (Gm.)	31.0	6.0	4.0
Peanuts (Gm.)	–	41.0	48.0
Corn flour (Gm.)	–	20.0	20.0
Wheat flour (Gm.)	–	6.0	8.0
Total calories	470	492	476
Total calories /protein calories	5.7	6.0	5.8

diets, but the risks would not have been justifiable.

Methods for weight and biochemical measurements. The children were always weighed naked. They were weighed on admission, and usually every day afterward before their first meal which was at 6 A.M. If they had had a continuous drip feed during the night, they were not weighed until 3 hours after the feed was finished. A direct-reading baby balance, correct to 10 Gm., was used.

Blood was taken from the internal jugular vein on the morning of the day after admission and every 7 days afterward, about 2½ hours after the first meal of the day. For the estimations that could not be made immediately, the serum was kept at –15° C.

The chemical methods were: for total protein, the gravimetric method of Van Slyke as described by King[6]; for total cholesterol, the methods of Zak, Dickenman, White, Burnett, and Cherney[7] and Zlatkis, Zak, and Boyle[8]; for amylase, the method described by King[6]; for pseudocholinesterase, the colorimetric method (with use of magnesium as an activator) of de la Huerga, Yesinick and Popper.[9]

The serum proteins were separated by paper electrophoresis with use of a barbiturate buffer of pH 8.6 with an ionic strength of 1.0. The stain was bromophenol blue. The curves were drawn on moderately thick paper on an E.E.L. scanner, and the proportions of the fractions were found by weighing the cut out areas under the curves.

Methods of analysis of results. A child who is responding favorably to treatment of kwashiorkor at first loses weight as he loses edema, then gains weight as he readjusts his body composition and builds new tissue. At the same time, the 4 constituents of the serum that were measured increase their concentration, not merely by a reduction in blood volume, but also by increased synthesis (as of protein and enzymes) or by release into the blood stream (as of cholesterol from the liver and other depots).[10]

After consideration of all our records, we realized that we must not only eliminate those children already mentioned, whose course was so complicated that we could not disentangle the effect of the complication from the effect of our dietary treatment, but must also adopt certain conventions. They were as follows:

A. Loss of weight. Loss was calculated as the difference between the weight on the day of admission and that on the day on which the lowest weight was recorded. If the lowest weight occurred on two days, the first of the days was assumed to end the period of loss. The minimum period of loss that was taken into account was 4 days. If the daily loss was more than 200 grams, it was omitted from the averages because it was thought to be due in part to factors other than the diet.

B. Gain of weight. This was usually calculated from the end of the period of loss to the end of the next 14 days or until the child was discharged from the hospital. If the diet was changed, the gain up to the time of the change was calculated, and a new calculation for the next dietary period was made. If the weight gain was interrupted by an obvious cause such as the start of an infection, the gain was taken only to the day before the interruption showed on the weight curve. A failure to gain for which no cause was found was taken to be due to the shortcomings of the diet and was included.

The minimum period of gain that was

calculated was 4 days.

Many of the children spent part of their stay in the hospital held in position on special beds while balance experiments were performed. Their changes of weight during the experiments were not included in the calculations.

C. Serum constituents. Changes were calculated only for periods in which the diet was unaltered. It was found that the changes in the first 14 days of treatment usually gave the most valuable information, and the later changes, except for those of protein fractions, were ignored. The calculations were simplified by the adoption of the practice of altering the diet on the days when the children were bled.

If the concentration of a serum constituent is high, alterations during treatment are difficult to interpret. It was therefore necessary to decide, somewhat arbitrarily, on figures for "high" concentrations and to omit all such figures from the means. The figures might be said to be approximate to "normal" values, but "normal" values have not been established for the local child population. The levels were 6.0 Gm. per 100 ml. of serum for total protein, 140 mg. per 100 ml. for total cholesterol, 100 units per 100 ml. for amylase, and 125 units per milliliter for cholinesterase.

The changes of weight and of all the serum constituents except the protein fractions were reduced to the mean per day to enable periods of different length to be combined. It was known that in some instances—the regeneration of serum proteins is an example—the rate of change was not always constant throughout the periods, but, since the data for all the dietary groups were treated in the same way, the errors were probably evenly distributed. To avoid minute quantities, the changes in the serum fractions were calculated as a single amount for the period of the first 14 days and another single amount for the period of the next 7 days.

The significance of means and of differences of means was examined by the t test, and values for t have been quoted where they appear to be informative. At the level of t that has been called significant, $P = 0.05$.

RESULTS

1. Clinical. The clinical assessments of progress have not been analyzed statistically, because they were too indeterminate and subjective.

The initial anorexia was most easily overcome by the milk diet, but this may have been largely because it was a thin fluid; solids and semisolids, such as the gruels made with the powdered biscuits, are always taken less readily than fluids by children suffering from kwashiorkor. The taste of Biscuit 8C seemed to be less well liked than that of Biscuit 15U, which was less nutty but more milky.

2. Intakes of protein, fat, and calories. The daily intakes are shown in Table VII. They were calculated in periods that coincided so far as possible with periods covered by the blood samples. The variations be-

Table VII. Mean daily intake of protein, fat, and calories

Diet	*Period**	*No.*	*Protein (Gm./Kg./day)*	*Fat (Gm./Kg./day)*	*Calories (Cal./Kg.)*
Milk	I	60	4.2	6.5	106
	II	40	4.6	7.2	125
Biscuit 15U	I	36	4.5	5.3	118
	II	34	4.8	5.7	129
Biscuit 8C	I	35	3.9	5.4	107
	II	25	4.5	6.3	127

*The length of Period I, as calculated for this Table, was from 6 to 10 days, and that of Period II, 7 to 14 days.

Table VIII. Mean daily loss and gain of weight during treatment

Diet	*Loss of weight*			*Gain in weight*		
	No.	*Gm./day*	*S.D.*	*No.*	*Gm./day*	*S.D.*
Milk	44	89.3	47.0	44	65.8	35.4
Biscuit 15U	24	99.9	61.8	34	68.6	19.1
Biscuit 8C	27	83.7	54.4	25	42.8	29.4
Test of difference of means						
Milk-Biscuit 15U		$t = 0.79$ (not significant)			$t = 0.42$ (not significant)	
Biscuit 15U-Biscuit 8C		$t = 0.98$ (not significant)			$t = 4.20$ (significant)	
Milk-Biscuit 8C		$t = 0.46$ (not significant)			$t = 2.72$ (significant)	

Table IX. Mean daily gains of serum constituents during treatment

Diet	*Total protein*			*Cholesterol*			*Amylase*			*Cholinesterase*		
	No.	*Gm./100 ml./day*	*S.D.*	*No.*	*Mg./100 ml./day*	*S.D.*	*No.*	*Units/100 ml./day*	*S.D.*	*No.*	*Units/ml./day*	*S.D.*
Milk	57	0.200	0.064	48	4.5	3.5	53	4.6	2.4	20	9.0	5.5
Biscuit 15U	29	0.175	0.061	27	3.7	2.0	24	4.1	2.6	32	8.5	6.1
Biscuit 8C	31	0.081	0.057	28	2.6	2.6	16	1.8	1.8	14	5.2	4.4
Test of difference of means												
Milk-Biscuit 15U	$t = 1.73$ (not significant)			$t = 1.08$ (not significant)			$t = 0.66$ (not significant)			$t = 0.27$ (not significant)		
Biscuit 15U-Biscuit 8C	$t = 5.90$ (significant)			$t = 1.72$ (not significant)			$t = 3.04$ (significant)			$t = 1.76$ (not significant)		
Milk-Biscuit 8C	$t = 6.88$ (significant)			$t = 2.46$ (significant)			$t = 3.52$ (significant)			$t = 2.06$ (significant)		

tween the dietary groups were not large. The small amounts of protein obtained from Biscuit 8C in the first period were a reflection of the difficulty of overcoming anorexia by use of that diet. In the later period, the protein and calorie intakes were approximately the same from all three diets, but the milk always provided more fat.

The children classed as having "severe" cases of kwashiorkor nearly all took smaller amounts than those classed as having "moderate" or "slight" cases. For instance, 33 of the 40 children with "severe" cases had the milk diet throughout treatment; their average daily protein intake was 4.23 Gm. per kilogram of body weight, and the 10 with "moderate" and 14 with "slight" cases, given the same diet throughout treatment, took 4.51 Gm. and 4.56 Gm., respectively.

3. Loss and gain in weight. The losses and gains in weight of the children in the three dietary groups are given in Table VIII. All three diets had much the same effect in causing loss of weight. Gain in weight was the same on the milk and Biscuit 15U diets, but was lower on Biscuit 8C. Of the 25 children on that diet whose data could be used, 5 failed to gain, and the average daily gain of the 20 others was only 51 grams.

The length of the period of weight loss depended, not on the kind of diet, but on the degree of severity. It was 8 to 10 days for the "serious" cases, 6 to 9 days for the "moderate," and 5 to 7 days for the "slight."

As indicated by the standard deviations, the range was wide for both loss and gain. Somewhat surprisingly, the losses and gains were the same in the "severe," "moderate," and "slight" cases.

4. Serum constituents. All the diets caused gains in the 4 constituents measured (Table IX). The mean values for Biscuit 15U were

consistently a little lower than those for the milk diet, but the differences were not statistically significant. Biscuit 8C was obviously much less effective than the other diets.

For the children who received the milk diet or Biscuit 15U throughout treatment, the serum proteins were separated electrophoretically, and the results appear in Table X. Although the changes in the first fortnight of treatment were large, they were not complete, and, where possible, the results of analyses for a further week have been included. They show a small continuation, in most fractions, of movements in the same direction as those in the first period.

The most striking feature was the increase in albumin, but the α_2 and β globulins also increased significantly. The two diets gave almost identical results. No effect that might have been due to the severity of the kwashiorkor could be detected.

5. The effect of high and low intake. The intakes of protein and calories per kilogram of body weight varied considerably, and the relationships of the intake to the loss and gain in weight and to gain in serum protein were assessed by regression equations. It was expected that the effects of increased intakes would be positive, and we were surprised to find that they were not. In no case did the regression lines have a statistically significant slope. The relation between protein intake and gain in weight for the children given the milk diet and Biscuit 15U is shown in Fig. 1.

For the biscuit diets, but not for the milk diet, higher intakes tended to be associated with larger gains in serum protein, but the probability that the effect was due to chance was slightly greater than 1 in 20.

6. The effect of changing the diet. The variations in weight during the treatment of kwashiorkor are so large that mean results obtained from small numbers of children given the same diet throughout are less revealing than the results obtained by altering the diets of individual children.

For 15 children the mean daily gain was 52 grams when they were first given the milk diet for about 10 days and 68 grams when they were afterward given Biscuit 15U. Biscuit 8C was given to 14 children on admission and for 5 to 14 days after and only 3 gained any weight at all. The diet was changed to milk, and all except one gained weight satisfactorily, the mean daily gain being 53 grams. Another 12 children were first given the milk diet, then Biscuit 8C, and finally milk again. The mean daily gains were 79, 20, and 68 grams in the three periods.

Table X. Total gain in serum protein fractions after treatment for first 14 days and next 7 days

		Albumin			*Globulins*								*Total*
					Alpha$_1$		*Alpha*$_2$		*Beta*		*Gamma*		
Diet	*Period**	*No.*	*(Gm./ 100 ml.)*	*S.D.*	*(Gm./ 100 ml.)*	*S.D.*	*(Gm./ 100 ml.)*	*S.D.*	*(Gm./ 100 ml.)*	*S.D.*	*(Gm./ 100 ml.)*	*S.D.*	*(Gm./ 100 ml.)*
Milk	I	26	1.65	0.50	0.02	0.23	0.20	0.20	0.38	0.20	−0.03	0.39	2.22
	II	11	0.56	0.79	0.24	0.16	0.06	0.21	0.11	0.20	0.01	0.28	0.72
Biscuit 15U	I	28	1.61	0.71	0.02	0.17	0.22	0.20	0.36	0.29	0.00	0.34	2.21
	II	22	0.35	0.47	0.02	0.13	0.07	0.28	0.10	0.25	−0.07	0.29	0.47
Test of significance of means†													
Milk	I		$t = 16.79$ (significant)				$t = 5.06$ (significant)				$t = 9.74$ (significant)		
	II		$t = 2.34$ (significant)				$t = 5.31$ (significant)						
Biscuit 15U	I		$t = 12.03$ (significant)								$t = 6.57$ (significant)		
	II		$t = 3.53$ (significant)										

*The length of Period I, as calculated for this Table, was 14 days, and, of Period II, 7 days.

†All other means are not significant and all differences of means between milk and Biscuit 15U are not significant.

The mean gains of the groups given Biscuit 8C were significantly less than those of the groups given the milk diet. The mean for the group given Biscuit 15U was not statistically different from the means of the groups given the milk diet.

DISCUSSION

The children on admission. So far as we know, the division of cases of kwashiorkor on clinical grounds into "severe," "moderate," and "slight" and the correlation with biochemical findings have not been attempted before. One good reason is probably that most of the centers where cases are collected are hospitals where children's beds are extremely scarce; thus, the only patients that can be admitted, and therefore the only ones investigated, must accordingly be those with what we would call "severe" or possibly "moderate" kwashiorkor.

The diagnosis of "severe" cases is obvious and presents no difficulty to the trained eye. The diagnosis of the less severe cases is very important from the point of view of public health and of the prevention of deterioration into the severe state. Simple means of diagnosis are needed, and weight for age has been suggested as a possibility, but our results show that in Uganda it cannot be used for diagnostic purposes with any certainty. It is obvious that a different situation exists in Mexico. There, the percentage that the child is below the standard weight is related not only to the other signs, but to the mortality rate.[2] Similarly, in Johannesburg, the highest mortality rate is among the children whose weights on admission are very low for the age.[11] The difference is almost certainly due to the absence, in Uganda, of severe gastroenteritis as one of the important adjuvants to the state of malnutrition. In Uganda, gastroenteritis and the marasmus it causes is seen fairly often in children

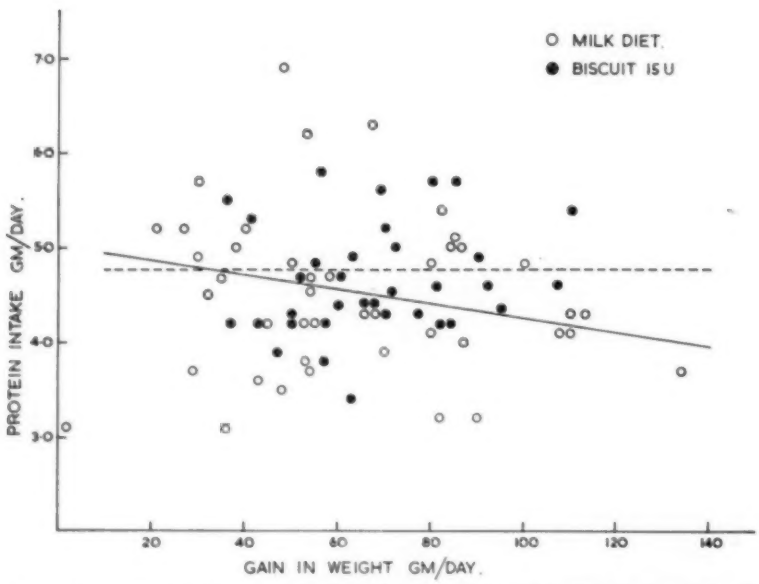

Fig. 1. The relation between protein intake and weight gain. The lines for the regression equations [for the milk diet, solid line: $Y = 66.25 - 3.94\ (X - 4.52)$ and for the biscuit diet, broken line: $Y = 68.38 + 0.0015\ (X - 4.76)$] have been included. Their slope is not statistically significant. It is also obvious by inspection that the higher intakes were not associated with greater gains.

under one year old, but after that age it is comparatively rare by itself and is rare also in association with kwashiorkor. Nearly all children admitted to our Unit for the treatment of kwashiorkor are said to have had short episodes of diarrhea, but the diarrhea seldom persists during treatment, and pathogenic organisms can very rarely be isolated from the stools. In contrast, stool cultures are positive in 28 per cent of the advanced cases in Mexico City, and fluid and electrolyte balance is regarded, no doubt correctly, as the most potent cause of death. Strictly speaking, mortality is outside our present terms of inquiry, although it is not altogether unrelated to condition on admission, but it is interesting that, of 544 children in Mexico City who weighed 60 per cent or less of the standard weight, 33 per cent died; in our Unit, of the 104 children with the same weight reduction admitted in the last 5 years, 12 per cent died. Our limited experience with severe kwashiorkor complicated by acute dehydration has convinced us that the dehydration is extremely dangerous.

The serum chemistry as a guide to severity. The serum analyses in Table III are unlikely to be of great value in assessment of severity in an individual case, because the variation to be expected, as the standard deviations suggest, is rather large. Usually, the "severe" cases showed values for total protein, albumin, amylase, and cholinesterase that were all very low. At the moment, nothing can be made out of the exceptions, or out of the more numerous aberrant values found in the "moderate" and "early" cases; the explanations might be extremely interesting.

The failure of the cholesterol to vary with the degree of severity is perhaps the only real surprise in Table III. The cholesterol level in our children is very labile, and, during treatment, seems to depend on the mobilization of body fat and the kind of fat in the diet.[12] Presumably, the level on admission varies for similar reasons. An attempt was made to correlate the level with the child's diet before admission, but it was unsuccessful; an exact record of the diet could never be obtained, and some of the obvious direct questions, such as whether or not any breast milk or cow's milk had been given, did not produce good evidence of a correlation.

Although the percentage of weight for age was the same for all the three grades of severity and although, presumably, that indicated approximately the same degree of hydration or overhydration in the three groups, it might be argued that the children who were most severely affected had the greatest dilution of their blood and had the lowest serum proteins because of that dilution. Against that argument is the fact that all the protein fractions were not reduced equally.

Perhaps the most that can be claimed for the values in Table III is that they conformed with the clinical distinction between "serious" and "slight" cases. Whether they should be used as an objective means of diagnosis is an open question. A combination of the low values for serum proteins, amylase, and cholinesterase can occur in very few conditions except "severe" kwashiorkor, and the values for protein, amylase, and cholinesterase in "slight" kwashiorkor were all lower than we find in children who have had a sufficient period of successful treatment.

The alterations during treatment. The chief interest in the losses and gains of weight during treatment (Table VIII) lies in the failure of Biscuit 8C to cause satisfactory gains. It seems that the ability of a diet to produce weight loss and to decrease edema cannot be a very critical test of the value of a diet intended for the treatment of kwashiorkor. Biscuit 8C, despite its success in this one direction, caused neither good gains of weight nor rapid changes in the blood chemistry. The changes caused by the milk diet and Biscuit 15U were very similar (Tables IX and X). The slight advantage consistently held by the milk diet was not statistically significant, but there was no doubt of the inferiority of Biscuit 8C.

The chief reason for the failure of Biscuit 8C probably resided in the quality of its protein. Because it contained less milk than Biscuit 15U, it contained less lysine, methionine, threonine, and valine, but most of the

deficiencies were small and unlikely to be of physiologic importance. It was found, however, by the direct chemical estimation of the Σ-amino groups of lysine, that the method of preparing Biscuit 8C with the skim milk cooked with the other ingredients caused a decrease of about 30 per cent in the "available lysine": the lysine was still present, but by combination with sugars had become unavailable for metabolic processes.[13] The lactose of the milk powder was thought to be largely responsible. Balance experiments with use of biscuit made with the milk either cooked in or added raw gave results that were consistent with those for the "available lysine." The retentions of nitrogen from Biscuit 8C and from another biscuit, with 15 per cent of the milk cooked in, were lower than those from similar biscuits in which the milk was uncooked.[1]

A significant gain in α_2 globulin (Table X) has not previously been reported. A gain up to the third week of treatment appears in data given by Demaeyer and Vanderborght[14] for children in the Belgian Congo, but it was followed by a loss in the next 5 weeks and was obviously thought of insufficient importance for comment. The gain might be related to changes in concentration of other serum constituents, such as lipoproteins or haptoglobins, which move in electrophoretic separation with the α_2 globulins. Alterations in the α_2 globulins are usually thought chiefly to represent variations in haptoglobins.[15]

The gain in β globulin is approximately the same as that found by Demaeyer and Vanderborght and also by Carr[16] in Southern Rhodesia. The significance of the change in the fraction is obscure; associations with the iron-binding capacity of the serum[17] and with the polysaccharides[14] have been suggested, and it is possible that the change may have some diagnostic value. A failure of the fraction to alter has been found previously.[14] If the differences related to severity in our cases on admission can be substantiated, it would be logical to expect alterations as the clinical condition improves. In the 54 of our children whose sera were fractionated, an alteration of γ globulin greater than 0.14 Gm. per 100 ml. (twice the standard error of the mean for this fraction) occurred in 34 at the end of 14 days of treatment, but no connection could be found between the alteration—which included gains up to 1.08 Gm. and losses up to 0.84 Gm.—and any of the other variants. Further investigation is obviously needed.

It is not possible to explain why larger amounts of the milk diet and of Biscuit 15U did not produce better results than the smaller amounts. The possibility that the increase of protein, or of any other ingredient, might be increasingly toxic, seems very remote. Friendly critics have pointed out that too much protein might be dangerous, but the range of 4 to 5.5 Gm. per kilogram of body weight, although more than may be needed for the maintenance of good growth in a healthy child, can hardly be called excessive for the repair of the severe protein depletion that is known to exist in kwashiorkor. Using this range, we have noticed that the blood urea is sometimes raised to between 30 and 40 mg. per 100 ml., but the rise is transient and does not seem to be noxious.

A more definite argument against a toxic effect is provided by the results of some of our experiments, not previously published, in which we used high-protein diets. When oil was first introduced into the therapeutic diets, it was added to mixtures of calcium caseinate, dried skim milk, and sugar that usually provided 6 to 8 Gm. protein per kilogram body weight. The mixtures gave excellent results, especially in the gain of weight, as Table XI shows. The "severe," and the combined "moderate" and "slight" cases are separated in the Table, and the patients with "severe" cases who had the high-protein diet also lost an extraordinary amount of weight.

The mean gains of weight of the children given the high-protein diet were significantly greater than those of the children who had the moderate-protein milk diet. The high-protein diet was less restricted in amount than the other, and the range of protein

Table XI. Comparisons of the effects of moderate and high protein intakes

Diet	*Grading of kwashiorkor*	*Loss of weight*			*Gain in weight*			*Gain in total serum protein*		
		No.	*Gm./day*	*S.D.*	*No.*	*Gm./day*	*S.D.*	*No.*	*Gm./day*	*S.D.*
Milk diet	Severe	27	89.6	43.0	23	69.0	43.6	33	0.198	0.063
	Moderate and slight	17	88.9	50.4	22	62.4	22.8	24	0.203	0.063
High-protein	Severe	21	125.1	34.1	27	94.2	42.0	23	0.219	0.018
	Moderate and slight	20	85.9	52.1	44	87.0	39.0	24	0.186	0.026
Test of difference of means										
Milk severe–high-protein severe		$t = 3.03$ (significant)			$t = 1.97$ (significant)			$t = 1.06$ (not significant)		
Milk moderate and slight–high-protein moderate and slight		$t = 0.16$ (not significant)			$t = 2.83$ (significant)			$t = 0.79$ (not significant)		

intake per kilogram was very large—from 4 to 10 Gm. A few children whose intakes were about 10 Gm. per kilogram gained weight slowly but gained more rapidly when the intake was lowered; apart from this observation, which was made so seldom that it cannot be regarded as proving anything, there was no sign of a toxic effect. The protein intakes of all the children were plotted against the weight gains, and, once again, there was no tendency toward a positive correlation. Unfortunately, the only constituent of the serum that was measured was the total protein. As Table XI shows, the rate of increase was high, but not exceptionally so.

The quality of the protein in the high-protein diet was exactly the same as in the other milk diet. In both diets, the protein was supplied by mixtures of calcium caseinate and dried skim milk in equal amounts. The ratio of total calories to protein calories was only 3.5 in the high protein diet against 6 in the other, but it is unlikely that the reduction was an advantage; the quantity of protein seems to be the only acceptable cause for the difference in the results. It is not, of course, entirely acceptable because of the absence of any effect that could be related to the gradient of the protein intake, but for an alternative explanation in terms of the diet we are driven into hypotheses for which no proof is yet available.

The simplest and most attractive of the hypotheses is that the two separate levels of gain are examples of the "dose-response" type of phenomenon, which is usually represented by a curve rising very slowly at first, then suddenly more rapidly, and then finally reaching a plateau. In the system that we are investigating, there may be more than one plateau: the first may be that for moderate protein intake and the second for the high protein intake. We are starting experiments designed to explore this possibility.

The extreme variability of the individual response makes the interpretation of any such experiments increasingly difficult and interesting. A very rapid gain of weight—provided, of course, that it is not merely due to the accumulation of edema fluid—presumably represents a concatenation of favorable metabolic events, and a failure to gain may be the result of delay in the completion of any of the events. We have had considerable experience in measurements of all kinds in children suffering from kwashiorkor, and the wide range of nearly every measurement never ceases to astonish. We should not, therefore, be astonished at the wide and apparently random variations of weight gains; they may be an oversimplification, for which a single mathematical expression is necessarily misleading, and they are certainly not random.

It may be that rapid weight gains can occur only if a certain state of protein repletion has been attained, and that repletion is more rapid on a high-protein diet than on

a low-protein diet. If that were so, the gains might be a critical test of repletion. Obviously, we need a measure for the degree of repletion. None of the serum estimations that we have used appears to be satisfactory for this purpose, and the best available method is probably the serial measurement of muscle nitrogen, as carried out by Waterlow[18] on biopsy specimens. The method, although admirable, is too difficult for routine use, and we are hoping to find a simpler method, based on the utilization of a standard diet and the excretion of its metabolites.

The optimal level for the protein in a diet intended to cure kwashiorkor or intended to ensure protein repletion, is of great practical importance. The experiments that have been described in this paper lead to the tentative conclusion that in the first days of treatment the loss of edema and rapid and desirable alterations in the serum chemistry can be brought about by small amounts of protein; for maximum gains in weight, however, large amounts of protein may be necessary. It would be interesting to know whether the large amounts must be given from the start of the treatment to ensure the most rapid possible repletion or whether they are only of value when a critical level of repletion has been reached.

SUMMARY

1. One hundred and thirty-one children admitted for the treatment of kwashiorkor and without serious complicating illness were divided, on clinical grounds, as having "severe," "moderate," or "slight" cases.

2. The criteria for the division are stated. Weight for age could not be used.

3. The children were given a milk diet or one of two kinds of peanut biscuit. All the diets provided 4 to 5.5 Gm. protein per kilogram of body weight per day.

4. The milk diet and one of the biscuit diets, which included 15 per cent dried skim milk added uncooked to the powdered biscuit, gave similar results. The other biscuit, which included 8 per cent of the milk cooked with the other ingredients, was less satisfactory.

5. Those children with "severe" cases took longer to lose edema (as shown by weight loss) than those with "moderate" or "slight" cases. No other effect of severity could be distinguished.

6. The weight gains that followed the loss of edema could not be correlated with the intake of protein. The gains of the children given the unsatisfactory biscuit were small. The gains of the children given the other diets were better but were less than those of another group who were given a high-protein milk diet.

7. The chief points discussed were: (a) severe diarrhea as a cause of the excessive weight losses found to accompany kwashiorkor in Mexico and elsewhere, (b) serum chemical determinations as an aid to the diagnosis of severity, and (c) the value of therapeutic diets and the magnitude and significance of individual variation in the responses to them.

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CLINICAL PATHOLOGICAL CONFERENCE

THE CHILDREN'S MEDICAL CENTER, BOSTON, MASS.

Sidney Farber, M.D., Editor
Gordon F. Vawter, M.D., Assistant Editor

THIS 11-day-old white female infant entered the hospital because of cyanotic spells and generalized twitching of 5 days' duration.

She was born following a full-term, uncomplicated pregnancy. The mother had been delivered of 3 normal children previously. Labor was spontaneous and without any difficulty. In the neonatal period, the child had normal respirations and normal color. The weight at birth was 7 pounds, 6 ounces. At 6 days of age, the baby was doing well on an evaporated milk formula when suddenly she was noted to have a 30-second episode of "jerky" rhythmic movements, which were definitely generalized and unaccompanied by cyanosis or urination. Four hours after this initial episode it recurred. The referring physician was notified and he was unable to find any evidence of abnormality at that time. During the next 24 to 36 hours the infant had 3 similar episodes; during one she became cyanotic. The referring physician was again consulted and at this time he heard a heart murmur. The child was admitted to a hospital where she was started on Digoxin. During the 3 days in the outside hospital, prior to admission here, the youngster had many seizures described as clonic in nature. Ten to 20 were observed each day, and all of them were accompanied by a moderate degree of cyanosis.

The family history showed that 2 older siblings had staphylococcal pneumonia and empyema 3 years prior to the child's admission to this hospital. One of the siblings died from the complications of staphylococcal pneumonia. A maternal first cousin has been followed at this hospital for congenital heart disease.

Physical examination disclosed the baby's weight to be 7 pounds, 8 ounces, length, 52 cm., head circumference, 34 cm., and blood pressure 45 mm./Hg. The baby was floppy and inactive and had a high-pitched cry. During several portions of the examination there were generalized seizures beginning with incoordinated thrashing of all extremities, followed by a cry and then by generalized clonic movements. These seizures lasted approximately 60 seconds. The temperature was 99° F., the respirations 28 per minute, and the pulse 160 per minute. Examination of the cranium disclosed no abnormalities. The pupils responded to light and the fundi were seen partially, but no hemorrhages were noted. Aside from micrognathia, the jaw and palate were normal. The heart showed a right ventricular impulse. There was a diminished second sound in the pulmonic area. There was a Grade III systolic murmur at the lower left sternal border.

Examination of the abdomen disclosed that the liver was palpable 1 cm. below the

costal margin. The spleen tip was just palpable. The neurological examination showed a poor suck reflex and no root reflex present; the Moro reflex appeared normal. There was no evidence of opisthotonus. The child was definitely sluggish. The reflexes were hyperactive.

Laboratory data on admission showed urine of pH 5.5, specific gravity, 1.012, and 1 plus albumin. Sediment was negative. White count on admission was 17,800, with about 80 per cent polymorphonuclear leukocytes. The hemoglobin level was 17.4 Gm. per cent. Lumbar puncture showed 7,300 red cells, 2 white cells, both of which were mononuclear leukocytes, a total protein of 229 mg. per cent, normal sugar, and no growth on culture. Blood chemistry determinations on admission disclosed a nonprotein nitrogen of 38 mg. per cent, a total protein level of 6 Gm. per cent, and calcium of 1.9 mg. per cent which, on the same serum specimen, was again reported as 1.1 mg. per cent. Phosphorus was 7 mg. per cent, and the fasting blood sugar level was 86 mg. per cent. A blood culture showed no growth. An electroencephalogram was abnormal for the infant's age. Electrocardiogram showed a sinus tachycardia with an adult R/S progression.

During her first hospital day the infant had frequent seizures and was started on Dilantin 30 mg. at once and 15 mg. every 6 hours. Paraldehyde, 2 ml., was also given immediately. The child was started on antibiotics. The seizures were not controlled.

Prior to the reporting of the blood chemistry results, 1 ml. of calcium gluconate was given intravenously. There was considerable bradycardia following this, but there was no demonstrable change in the pattern or frequency of the child's seizures. The following day the child's condition deteriorated severely. She had many more seizures, became less responsive, and gradually but progressively became worse. She died without any evidence of congestive heart failure. The blood calcium level, obtained at the time of death, was 3.6 mg. per cent.

In the hospital, respiratory rates were 36 to 40 per minute and pulse rate 180 per minute. Chest x-ray suggested atelectasis of the left lower lobe.

DR. FRANCIS X. FELLERS.* In summary, we are presented with a young infant under 2 weeks of age who, at the age of approximately 6 days, began to have seizures or rhythmic convulsive episodes, later associated with cyanosis. The presence of a loud cardiac murmur with other cardiac changes suggests some sort of congenital cardiac lesion. The course was progressively downhill in spite of therapy directed against the seizures. The child eventually died at 12 days of age and the final important serum analysis demonstrated only a hypocalcemia. Since the small jaw was described, I suppose one should consider some form of facial dysostosis, although no other lesions specifically associated with this are remarked upon, for instance, strabismus or cranial synostosis.

Were the seizures and hyperirritability which this infant presented secondary to hypocalcemia? We have three serum determinations in which the calcium level was very low. Actually, these values are so low that on looking through the literature, I have not found any comparable values. The lowest I found was one reported as 3 mg. per cent in a child with pseudohypoparathyroidism, reported by Gribetz,[1] where the initial serum calcium level was 4, one within about 1 hour was 3, and one after another hour was 4. I just talked to Dr. Jonathan Cohen and the lowest he recalls is about 4 mg. per cent. I suppose this could be a new chemical finding. I think we have to eliminate several things before we accept this as a true value for serum calcium, that is, below 2 mg. per cent. Blood taken from children could be placed in an oxalated tube by mistake. Certainly those tubes which one uses for nonprotein nitrogen determination contain oxalate, and if a calcium level were then determined on this sample by usual methods, no calcium, or very little, would be found. The method commonly employed utilizes oxalate precipi-

*Dr. Fellers is an Assistant Physician at The Children's Medical Center and Associate in Pediatrics, Harvard Medical School, Boston, Mass.

tation for calcium and this may give a low blank reading, even though no calcium is present. However, I think that this is not the case here.

Second, was the blood allowed to sit for any length of time? Dr. Harrison calls our attention to the fact that the pH of blood standing at room temperature will rise rapidly. That is, the CO_2 dissolved and liberated from H_2CO_3 is lost to the atmosphere. Since calcium and phosphorus in serum are actually nearly at levels of saturation, a change in pH might be sufficient to allow calcium phosphate to precipitate, and calcium would not be found subsequently. This process begins in about one hour.

Before we accept these results as reliable, we should recall those factors which control levels of serum calcium. Serum proteins bind about half the calcium. Most of the other half is ionized but about 0.5 mg. per cent is in a diffusible but nonionized form such as calcium citrate. In severe renal damage this fraction may be highly elevated. Here the serum protein level was close to normal at 6 Gm. per cent. The McLean-Hastings nomogram for determining the bound calcium and the diffusible ionized calcium levels does not go down to this range. Dr. Ko repeated some of these determinations on the same specimens and obtained values of the same order of magnitude. Moreover, he found that the final serum sample contained 14 mg. per cent phosphorus. The serum potassium in both specimens was between 4 and 5 mEq. per liter, so that there is certainly not a great hemolysis to account for change in the serum phosphorus. Since the values for hypocalcemia have been consistent, I think we do have a hypocalcemia, but whether it is at a level as low as 2 or 3 mg. per cent is open to question. Experimentally, we have varied serum phosphorus, as well as serum calcium, a great deal by phosphorus infusions and loading techniques. In rats with serum phosphorus up to 60 mg. per cent, I have never seen a serum calcium level below 4.1 mg. per cent. In one child, phosphate loading procedures brought the serum phosphorus levels up to 28 mg. per cent in the presence of normal kidney function, and the serum calcium level was still 7 mg. per cent. Under these circumstances there was no tetany. In rats in which the serum calcium level was 4, there was severe tetany. In severe renal failure, where phosphorus may rise to 18 mg. per cent, the serum calcium drop is usually to a level around 6 mg. per cent. When secondary hyperparathyroidism occurs, the values are lowered to a lesser degree. Perhaps this is not pertinent in this instance.

Now I would like to know about the electrocardiogram, if this information is available.

Dr. Anna Hauck. I have remeasured the timing, which is difficult with a rate of 200 per minute. The P-R interval and QRS duration are normal, but the Q-T interval is definitely proportionately prolonged.

Dr. Gordon F. Vawter. An electroencephalogram is reported as showing low voltage and little electrical activity, without localized abnormality or signs of diffuse cortical disease. An electrical activity pattern came through which closely simulated patterns of electrocardiographic function, which I gather is another way of describing the diminished cortical activity.

Dr. Fellers. We are faced with the differential diagnosis of hypocalcemia in an infant. Clinically, we have evidence of hypocalcemia with the seizures and with EKG findings. The cry also was shrill. There apparently was no Chvostek sign, however, and there was no papilledema; papilledema may often be associated with hypocalcemia. Could this be tetany in the newborn period? We would include both the tetany which occurs within the first 2 weeks of life and that which is the so-called tetany within the first day of life. Could this infant be a victim of maternal hyperparathyroidism, associated with a primary adenoma of the parathyroid, or possibly following a secondary hyperparathyroidism, say from severe renal disease? This is not likely since we have nothing to indicate any maternal disease. The initial serum phosphorus value would not be compatible with such a diagnosis because

the value is not low enough to indicate it. With hyperparathyroidism in the mother, the activity of the infant's parathyroid glands would be decreased so that the child would have an acute hypoparathyroidism immediately following birth. Also, this is not likely since symptoms developed relatively late.

Would this be so-called idiopathic primary hypoparathyroidism? I do not know of any instances of this at this age.

Another unlikely possibility is maternal osteomalacia. Snapper[2] has reported that in the Orient the maternal supply of calcium is often so low that a child may be born with a deficit of total body calcium. With growth, what calcium is available in the extracellular phase is rapidly laid into bone and so may lead to hypocalcemia with low phosphorus and the whole sequence of rickets.

I think that tetany of the newborn is the most probable explanation in the present instance. This disease was initially described in 1913 and since has been well documented.[3] The primary disorder appears to be phosphorus retention and the hypocalcemia is a secondary phenomenon.

Now we should consider whether the phosphorus retention is a result of a primary decrease in renal function, whether it is related to a very high phosphorus intake, or whether it is related to a functional hypoparathyroidism. Dr. McCrory and co-workers[4] have demonstrated decreased glomerular filtration rates in newborn infants. Therefore, decreased renal function may be involved. Infants fed normal human breast milk usually do not develop tetany of the newborn. It has occurred but is very unlikely. The phosphate content of cow's milk is approximately 1.0 Gm. per quart and of maternal milk, only 0.2 Gm. per quart, so that phosphate load may constitute an important aspect also. Certainly almost all the documented cases of tetany in the newborn have been associated with the use of cow's milk in evaporated milk formulas. This child received evaporated milk at home and here in the hospital. If it is assumed that this was the usual formula prescribed, we have a second factor which may be implicated in this particular infant.

Third, whether or not there is the factor of relative parathyroid hormone inactivity or unresponsiveness, I don't know. Dr. McCrory[4] has demonstrated that both in normal newborn infants and in those with tetany, there is a response to intravenous parathormone and in a small dosage of 15 units. Also, if one restricts the phosphorus intake of these infants by giving them aluminum hydroxide, as in Amphojel or Gelusil, which binds phosphorus in the intestine, these infants can reabsorb phosphorus in the kidney. These studies also suggest that the kidney can respond to parathormone. I do not think we have any evidence to indicate whether there is actual parathormone circulating in these infants. This type of analysis, I suspect, will have to be done eventually.

Recently there has been an increased interest in the pediatric literature concerning so-called tetany in the first 1, 2, or 3 days of life. Dodd[5] in 1949 called attention to the fact that hypocalcemia may occur within the first day or two of life and is often associated with a low serum phosphorus level. It has been described further recently by Gittleman and co-workers.[3]

The ascribed cause might possibly implicate vitamin D, perhaps in a paradoxical effect, but I think we should consider it. The babies who have this syndrome usually have received evaporated milk with vitamin D added or have had additional vitamin D preparations at an early age. Infants who have had breast milk only, or who have had evaporated milk or whole milk preparations without added vitamin D, have not had this syndrome. The explanation may be that in these infants vitamin D apparently makes calcium and phosphorus readily available. Since the skeleton can avidly accept calcium and phosphorus for laying down bone, there could be a rapid utilization of extracellular calcium and phosphorus. One more possibility should be considered. In a normal infant (as normally in all of us) there is a continuing resorption of the bone which is apparently under control of the parathyroid

hormone. We know, or at least it has been suggested within the past 2 to 3 years, that one of the rate-limiting factors of calcium control is the rate of calcium resorption from the bone, and it might just be that this rate limits the amount of calcium which is then available for redistribution into the extracellular space. One can suggest, then, that this rate limitation of bone resorption may be a related factor.

In the final diagnosis, this infant probably had a cyanotic heart disease. The elevated leukocyte count and the suggestion of pulmonary atelectasis probably represent an infection, perhaps following regurgitation or vomiting from the seizures. Finally, we still must speculate as to the exact type of hypocalcemia. It may be tetany of the newborn, with a decreased glomerular filtration, increased phosphate load, and possibly the additional factor of a rate-limiting process of absorption of the bone. I suspect that we will find that the parathyroid glands were normal.

Dr. Richmond Paine. I do not know what this will turn out to be, but I do not believe that the three extremely low calcium levels can be ignored or that this is infantile hypocalcemic hyperphosphatemic tetany, with such a low calcium value. The onset of convulsions in 6 days is, in itself, intriguing, because there are not very many conditions that produce them at that age. Congenital cerebral anomalies, I think, rarely produce them until the child is several months of age. At that time, cerebral function, that is, hemisphere function, becomes evident. The earlier neonatal seizures are based more readily on birth anoxia or trauma with direct brain insult or some congenital metabolic defect such as the "maple syrup" urine disease which Mencke first described from this hospital some years ago. Those defects, however, produce seizures within the first few days. There are only about three things which I can think of, aside from birth injury or anoxia, that will produce them at 6 or 7 days of age. Ordinary tetany is the most obvious and by far the most common. A second is pyridoxine dependency, not pyridoxine deficiency, but a much rarer dependency in which a few days are required for the store of maternally derived pyridoxine to be exhausted sufficiently to produce difficulty.

Another is a rare syndrome with convulsions on the sixth day of life in 3 siblings reported by Joseph in Paris a year ago. There was normal calcium reported but a spinal fluid protein level as high as 224 mg. per cent.

One other possibility, which I do not understand fully, is a case which Fanconi reported in a Swiss journal in 1953, which he called cerebellum-related hypocalcemia and tetany. This infant began to have intractable convulsions some time between 7 and 10 days of age. The serum calcium was 1.9, which struck me as being the lowest calcium level I had ever heard of, and when the baby died the autopsy showed microcephaly, internal hydrocephalus, and cerebellar hypoplasia. There was also a cyst in the septum pellucidum, which was probably coincidental. He did not record any renal or parathyroid abnormality, but I should almost have thought that there would have to be a functional one in order to explain this. I do not see how the cerebellar abnormality alone would reduce the calcium to such a level. It is true that osmoreceptors in the supraoptic nuclei of the hypothalamus and the tuber cinereum do control the electrolyte metabolism for sodium and potassium to some extent, but I do not know of any proof of influence over calcium. I am mystified about this.

Dr. Jonathan Cohen. Two observations from the experimental laboratory might be of interest here. One pertains to parathyroidectomy in rats. If one removes the parathyroid in weanling rats, they can be kept alive by giving them a high calcium diet until they are mature. Their serum calcium level will average between 4 and 5 or 4 and 6 mg. per cent, and the serum phosphorus level will not become elevated to more than 8 mg. per cent. An animal whose parathyroid has been removed completely would have a higher calcium level than this child did.

The second point is that if one takes the blood of a dog and sends it through a col-

umn which will remove calcium, the blood calcium of that dog can be reduced to about 2 mg. per cent and kept at that level for about 6 hours, at which time the dog will die of parathyroid tetany. If it is kept at a level of about 3 or 4, one can keep the animal alive for the length of the perfusion. In either case, if either the dogs or the rats are sacrificed, one finds no pathologic conditions.

I wonder if Dr. Fellers would tell us if he expects to find any abnormalities on this postmortem, and, second, I would like to ask Dr. Shwachman whether he has any remarks to make on the method by which these blood calcium levels were determined. It could make quite a difference.

Dr. Fellers. I doubt if you would find many abnormalities. Certainly I don't know of any that might be related to hypocalcemia, apart from hemorrhage into the soft tissues.

Dr. Harry Shwachman. This is the lowest calcium level I have ever seen, and frankly, I don't know how reliable it is since, with such low concentration, an error in a fraction of a drop in titration will give one a difference of 0.5 mg. per cent.

Dr. John Crigler. Is it an accurate statement that the child received 1 c.c. of calcium gluconate before death?

Dr. Sherwin Kevy. That is correct.

Dr. Crigler. Can you tell us why this dosage was not repeated or a larger dosage was not given, since the amount administered could not have changed such a low calcium level very much?

Dr. Kevy. The heart rate dropped precipitously and remained very slow for some time, after even this small dose.

Dr. Sidney Kibrick. Would Dr. Fellers comment on neurological findings (reflexes and lumbar puncture) in a child with hypocalcemia?

Dr. Fellers. This brings up one point. Often signs of hypocalcemia may be minimal, depending on what the other serum electrolyte levels are. We do not know what the rest of the serum compartments or parameters really were. Whether one can get these findings in cerebrospinal fluid just from continuous seizures, I do not know. We have evidence suggesting hypoxia, however. Another point of interest: what is the relationship of the level of calcium in spinal fluid to seizures in the newborn? I don't think we have any answers on this as yet.

Dr. Charles A. Janeway. I would like to ask Dr. Fellers just a few more questions. The problem of seizures in relation to calcium, as I understand it, involves a number of factors. Calcium, magnesium, sodium, and potassium all have a place in this problem, as does carbonate which depends on the pH. In a patient with a very low calcium level, can some of this deficiency be made up by magnesium which is partly antagonistic?

The second thing I wonder about, in view of the phosphorus levels, is this—could the infant be dying of renal failure?

Dr. Fellers. Dr. Ko did determine serum magnesium levels on this infant. The initial serum magnesium was 1.5 mg. per cent and the one at postmortem was 2.2 mg. per cent. I think these are probably just barely within the limits of our normal, which is about 1.6 to 2.3 mg. per cent. Certainly magnesium could play a part in tetany. Normally, in rachitic tetany, the serum magnesium level is often on the low side, but not extremely low. I do not know of any very clearly demonstrated cases of tetany with a pure and simple low magnesium level. We have been most interested to know whether this actually does exist, and certainly in a nephrotic patient the serum magnesium level goes down to 0.5 mg. per cent without actual seizures. What is absolutely necessary for the development of tetany remains unclear. What about the report of serum phosphorus of 14 mg. per cent? It may be that there is a complete loss of cellular integrity and not necessarily any element of renal failure.

Dr. Crigler. We had 4 patients with neonatal tetany, and laryngeal spasm and cyanosis always worried us. These patients did not always respond to calcium, but at least the calcium did help. The serum calcium level would remain low despite calcium therapy, and the patient symptomatically would get better during this newborn period. If this child had such a low calcium serum

level, there must have been an almost imperceptible ionized calcium level. One would expect a Trousseau's sign or some carpopedal spasm and would, therefore, concentrate a bit more on calcium replacement despite the bradycardia which might occur with an injection of calcium gluconate. We now have, in the Metabolic Unit, a child 14 years of age who has what appears to be idiopathic hypoparathyroidism, but she also has an associated skeletal abnormality including micrognathia, some changes in the clavicle, and very badly misplaced scapulae. She had tetany of the newborn and was studied in the interim between the newborn period and the present time, with very nicely documented normal tests for parathyroid function and for calcium studies, when she was 4 years of age. I wonder if she may not represent the type of tetany seen in the newborn period, superimposed upon some abnormality of parathormone synthesis or something of this type. Perhaps the results in this patient might have been more like those in the other child if she had lived.

Fig. 1. A tiny nodule of parathyroid tissue lies in pharyngeal submucosa. (Hematoxylin and eosin. ×150.)

Dr. Farber. We would like to hear from the House Staff.

Dr. Sherwin Kevy. The house staff diagnosis on admission was congenital heart disease, most likely tetralogy of Fallot, and also organic brain disease, cause uncertain. We were doubtful of tetany of the newborn and doubtful of parathyroid disease.

Dr. Farber. Dr. Vawter, will you describe the pathologic findings?

Dr. Vawter. This patient has multiple congenital anomalies, most of them being an absence of one thing or another or deficiencies in structure. They range from uncomplicated absence of the gall bladder through a cardiac configuration which falls into the pattern of tetralogy of Fallot (with a large ventricular septal defect, a very small bicuspid pulmonary valve, and absence of the ductus arteriosus) associated with a degree of hypoplasia of the lungs. There may be other absences or deficiencies. The hypoplastic and ectopic thymus lay high in the neck and weighed about one-fifth of what one would expect. This was associated with hypoplasia of the jaw. We searched carefully for parathyroid glands. We have sectioned completely the thyroid, the thymus, and most of the structures of the neck but found no parathyroid in these tissues. We did finally find one parathyroid gland which was ectopic and hypoplastic. This was high in the submucosa of the posterior pharynx (Fig. 1). There was a very small group of parathyroid cells which were of a water-clear type and larger in their volume than one expects. This is a very, very small gland, indeed. The site is not an unusual one for ectopic parathyroid glands. Dr. Flake and others have removed a parathyroid during a tonsillectomy on a patient previously operated upon for a branchial cleft sinus on the same side.[6] This misplacement of tissue is theoretically of great importance in terms of the embryogenesis of parathyroid glands. There are

other possible ectopic sites for parathyroid glands. They have been described up and down the neural structures of the neck, and have been described as being related to the phrenic nerve, deep in the thorax.

One has to be quite courageous, therefore, to present a case as absence of the parathyroid gland. The present instance, however, does seem to come quite close to such a condition. The relationship which Dr. Crigler has pointed out, with the small jaw and difficulties with parathyroid glands, seems to be quite important because this is a recurring theme in the few cases in the literature where parathyroid glands have been hard to find. Either the patient has been an anencephalic monster, has had acrania, or has had obvious abnormalities of the jaw and structures of the upper neck.[7] It is possible that this patient did have a deficiency of parathyroid tissue, associated with ectopia, and that this at least contributed in part to the development of the hypocalcemia.

This child had a lesion in the brain which consisted of degeneration in the middle laminae of the cortical neurones (laminae 3 and 4 principally) associated with an increase in glia in the immediate vicinity. This type of degeneration in the brain (which was of normal weight) may follow anoxia or shock, and it is possible that it developed in relation to the cyanotic episodes. One wonders whether this type of lesion has something to do with the calcification which may be found in the basal ganglia or, much more rarely, in the cerebral cortex of patients with hypoparathyroidism.

At autopsy, our bacteriologic studies were essentially unrevealing, but there was a considerable degree of both atelectasis and chronic pneumonia in the lungs, which I believe had an aspirational basis. The bones and the kidneys were within histologically normal limits.

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COMMENTS ON CURRENT LITERATURE

The mechanism of tick paralysis

TICK paralysis is an acute ascending flaccid paralysis which may terminate in respiratory failure. It affects both animals and human beings, and is caused by the bite of the female tick which is believed to introduce a neurotoxin secreted by its salivary glands during feeding. This so-called "tick-bite disease," characterized in some instances by fever as well as paralysis, was first described by Howell in Australia in 1824. It was first reported in North America by Todd[1] in 1912. Prior to 1938, all reported cases of tick paralysis in human beings in this country had been located in the far western states, Montana, Idaho, Oregon, and Wyoming, and the adjoining southwestern regions of Canada, areas in which the wood tick, *Dermacentor andersoni,* is indigenous. In 1938 Robinow and Carroll[2] reported a case from Georgia. This was the first case recorded in the East or South and apparently the first instance of tick paralysis following the bite of the common dog tick, *Dermacentor variabilis.* Within the next few years 128 cases were reported from the northwestern states and 25 from the southeastern and Atlantic seaboard states.[3, 4] The disease has been reported consistently from 6 states of the Rocky Mountain area: Colorado, Idaho, Montana, Oregon, Washington, and Wyoming. A few cases have been found in Texas in the Southwest, in New York and Pennsylvania in the Northeast, in 7 states of the Southeast, Alabama, Georgia, Kentucky, North and South Carolina, Tennessee, and Virginia, and also in the District of Columbia. By the early 1950's over 300 cases had been reported in the United States and Canada, with a mortality rate of approximately 12 per cent. In 1954 Jaffe and Perlmutter[3] described what was believed to be the first case recorded in the state of Florida. The tick incriminated was *D. variabilis,* and the authors emphasized the fact that the case occurred during the month of November and that this species is prevalent in the southern states throughout the entire year. In the 5-year-old child described, severe headache, stiffness of the back and limbs, and inability to walk led to the initial diagnosis of poliomyelitis.

While the disease is essentially one of infancy and childhood, tick paralysis has occurred also in adults. The patient is usually very irritable, and experiences general malaise and anorexia for 12 to 24 hours preceding the onset of paralysis. In somewhat older children paresthesia and pain in the lower extremities may be the first definite complaint. Incoordination of the lower extremities is followed in a matter of several hours by a symmetrical flaccid paralysis. Rapid progression of the paralysis is characteristic of the condition: a more or less complete symmetrical flaccid paralysis of the Landry type, extending upward to involve the arms and neck. Signs of bulbar paralysis, dysphagia, dysarthria, lingual and facial paralysis become marked and the patient may die of respiratory paralysis. The same ascending progression is seen when the cranial nerves are involved. The sternomastoid, trapezius, tongue and pharyngeal muscles become involved first, then the face and extraocular muscles; respiratory paralysis and death follow. If the tick is not removed,

this progression may cover a brief span of from 12 to 24 hours, depending upon the amount of toxin being elaborated and, to some extent, upon the site of attachment of the tick. Experimental studies indicate that ticks vary in their ability to produce the toxin; some apparently produce very little, or the substance elaborated is less specifically neurotoxic. Physical examination of an affected child on admission to the hospital reveals a flaccid type of paralysis with absent deep and superficial reflexes. The diagnosis of anterior poliomyelitis may appear to be the most obvious one. In the absence of bulbar signs, the temperature, pulse, and respiration are usually within normal limits. Urinalysis and urine culture, blood culture, and spinal fluid findings are uniformly negative. There are no significant changes in the white cell count or in the differential count.

Thorough search for the tick and early removal are of great importance; common locations for attachment are the scalp, ears, neck, axillae, and the groin. In girls especially, a tick attached to the scalp may be overlooked if the hair is long and thick. Of the total number of cases recorded, more than half have been in girls and women, in spite of the fact that their activities take them into wooded areas less frequently. The female tick which elaborates the causative toxin remains attached to the body for 10 days, or less, to 2 weeks, and is said to inject the largest amount of toxin about the fifth to the sixth day of attachment.[5] There appears to be a direct relationship between the site of attachment of the tick, the length of the incubation period, and the severity of the paralysis in that close proximity to the central nervous system shortens the incubation period and increases the severity of the manifestations.[6] With removal of the tick, rapid clearing of the signs and symptoms follows, and recovery is usually complete within 3 to 4 days. Where the bulbar type of paralysis is present, a respirator may be needed, as well as mechanical suction to clear the airway. In a few instances recovery has been slow, and muscular weakness may be present for from 3 to 4 weeks after removal of the tick. In one case recorded the child did not improve as expected and died 2 days following removal of the tick.[5] Care should be exercised in the removal since pressure on the tick may express still more toxin from the salivary glands into the patient's blood stream and since it is necessary that the head with its hypostome be removed intact. Various means of removal have been employed: the application of petroleum jelly or oil which interferes with the air exchange of the arthropod, the application of ether, chloroform, kerosene, gasoline, or heat to encourage withdrawal, or, where necessary, excision of the skin to which the tick is attached. Experimental investigations have shown that the toxin is present in the saliva of the female tick and in her eggs. An extract of the eggs of both *D. andersoni* and *D. variabilis* produces paralysis and death in mice within 24 hours or less.[5]

Until recently little was known as to the mechanism of tick paralysis or the nature of the toxin elaborated by the salivary glands. In this connection an experimental study reported in the Feb. 12, 1960, issue of *Science* is of special interest. This report by Murnaghan[7] of the Department of Pharmacology, University of Ottawa, Canada, describes a neurophysiologic study carried out on dogs which were paralyzed by the application of ticks, in this case, *D. andersoni.* The condition produced in dogs resembles closely that which occurs in the human subject. In the animal severely paralyzed, the muscles are flaccid and the tendon reflexes are absent. The anterior tibial muscle was selected for special study because it appears to be involved early in the paralysis. Previous investigations by Murnaghan had shown that during paralysis this muscle will respond to direct electrical stimulation but fails to contract when stimulated through the peroneal nerve. This finding was interpreted to mean that "the motor nerve fibers could not conduct a nerve impulse, or that there was a block at the neuromuscular junction."[7] On stimulation of the sixth lumbar

ventral root, an action potential from the peroneal nerve was recorded indicating that motor nerve fibers were conducting an impulse. The muscle which did not respond to nerve stimulation did contract when acetylcholine was injected into the artery supplying the muscle; in fact, the paralyzed muscle exhibited an increased sensitivity to acetylcholine, a condition which is seen in denervated muscle. The response to acetylcholine, to antagonists of blocking agents, and to repeated stimulation suggested to the author that this type of paralysis does not resemble that brought about by blocking agents such as curare or decamethonium, or by excessive doses of anticholinesterases, but that it is similar to the type of paralysis seen in poisoning by botulinum toxin. Studies with perfused muscle preparations verified these findings, and Murnaghan concludes that the paralysis "produced in the dog by the wood tick, *Dermacentor andersoni* Stiles, is due to failure in the liberation of acetylcholine at the neuromuscular junction because of a conduction block in the somatic motor fibers produced by the tick toxin."

Such studies as these by Murnaghan are of interest not only from the standpoint of neurophysiology, but also from the clinical point of view in tick paralysis, since they reemphasize the need for early removal of the tick. In few diseases which are potentially serious and even may end fatally, is recovery so dramatic once the source of the toxin is removed.

RUSSELL J. BLATTNER

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PEDIATRIC PROFILES

*James Lawder Gamble**

(1883-1959)

WHEN James Lawder Gamble, Professor Emeritus of Pediatrics, died of a cerebral hemorrhage on May 28, 1959, the Harvard Medical School lost one of its most distinguished alumni and beloved faculty members. Born the son of a gentleman farmer on July 18, 1883, in Millersburg, Bourbon County, Kentucky, he received his elementary education in the Millersburg Female College and his secondary schooling at Millersburg Military Institute. After his graduation, the family moved West and he entered Stanford University, from which he received his B.A. in 1906. He selected Harvard as his medical school and graduated cum laude in 1910. Following a 2-year internship in medicine at the Massachusetts General Hospital, where he admired the sartorial elegance and clinical acumen of Dr. Fred Shattuck and enjoyed the companionship of some of the future leaders of American medicine, he took 6 months of pediatric training at the Children's Hospital, then on Huntington Avenue.

In 1913, his hospital training completed, Dr. Gamble set off for Europe, where his visits to outstanding clinics in Austria and Germany impressed him with the possibilities of applying quantitative chemical and physiologic methods to the study of disease. Returning to Boston, he learned the new methods being developed by Otto Folin and Francis Benedict and began his investigative career under Dr. Fritz Talbot at the Massachusetts General Hospital. It was during this period at that hospital that he formed an enduring friendship with Walter W. Palmer (M.D., 1910) and, through him, fell under the spell of Prof. L. J. Henderson, whose physicochemical approach to physiologic processes made a deep impression on him, which he described in the following sentence:

"Although I never worked directly with Henderson, I learned from him to admire the beauty of the physico-chemical systems which sustain the body fluids, the marvel of their automaticity and their remarkable resiliency in the presence of obstacles imposed by disease, and ever since I have been content to work in this wide field as an humble artisan applying the simple tool of quantitative description to the pattern provided by this great architect of concept."[1]

Perhaps unconsciously, not only his approach to scientific problems but his pattern of scientific living were influenced by Henderson; it may well be that Gamble's self-imposed isolation from clinical responsibility, so similar to Henderson's aloofness from the actual performance of experimental work, made possible the clarity and elegance of his subsequent studies.

In late 1914 he was invited to join the new full-time Department of Pediatrics at Johns Hopkins. Here, between 1915 and 1922, he began some of his fundamental investigations, met Kenneth Blackfan with whom his life was to be associated so intimately later at Harvard, and decided to give

**This Profile of Dr. Gamble was prepared as a Memorial Minute to be presented to the Faculty of Medicine of Harvard University at its meeting March 4, 1960, by a Committee consisting of Dr. Charles A. Janeway, chairman, and Drs. Allan M. Butler, John F. Enders, A. Baird Hastings, Thomas H. Lanman, and George Nichols, Jr.*

up all clinical responsibilities in order to devote his life "to the study of disease by the methods of chemistry." This decision, which his Chief, Dr. John Howland, who was devoted to him, considered unwise at the time, set the course of his career.

There was one brief flurry of clinical activity during World War I when he was placed in charge of the health of a group of French refugee women and children in an old chateau near Versailles. He used to enjoy describing the horror of the good sisters of this institution who, upon discovering that the young American physician had prescribed fresh air for their charges by surreptitiously opening the windows, would rush through the dormitories closing them and shouting, "Courant d'air, courant d'air!"

Returning to Baltimore, Gamble plunged into his life's work as a student of disease. He described his years at Johns Hopkins in his characteristically disarming manner, as follows:

[Howland] "gave a young, ill-trained, would be investigator place in his fine new chemistry laboratory and sustained his courage by a kindly disregard of his first fumbling efforts. This laboratory was the first one in this country for study of disease in the clinic by quantitative methods of chemistry. It was the consummation of John Howland's clear vision of the value of such equipment in a university department of medicine. He brought a brilliant young biochemist from St. Louis to set it in motion. The ebullient McKim Marriott lost no time about this. Under the impact of his gay enthusiasm the laboratory immediately became importantly productive. Dr. Howland had a boyish pride and joy in his laboratory. He often worked there himself, carrying out some measurement which Marriott had assigned him. He enjoyed the challenge to accuracy of performance in a complicated analytical procedure and was greatly elated when he scored par on a theoretical solution. Those of us of the laboratory group at the Harriet Lane never thought of him as 'The Chief.' His attitude was that of an approving elder companion in the entertaining pursuit of new information by the methods of chemistry. We were expected to make our own choice of features of disease to assail by approach of our own devising. So there was in his laboratory a happy lack of program and a delightful spirit of free adventure.

"The establishment of the laboratory came opportunely at the beginning of the era of micromethods of measurement which greatly facilitated examination of biochemical events in patients. Clinical medicine was being given a large new armament and it was exciting to find that these methods which were being developed by Folin, Van Slyke, and others made information we were after easy to come by. Moreover, we had in our midst a versatile inventor of micromeasurements. The study of the processes of acid-base metabolism during fasting, which Graham Ross, Frederick Tisdall, and I carried out, would not have been possible without the methods for measuring sodium, potassium, calcium, and magnesium which Benjamin Kramer's ingenuity gave us. The fruitful studies of rickets and tetany by Howland and Marriott and by Howland and Kramer were also implemented by these methods. I am glad to have this opportunity to acknowledge the laboratory's large debt to Benjamin Kramer.

"In those primitive times the luxury of technicians for young investigators was unheard of. Marriott however did manage to provide himself with a technical assistant by an illicit arrangement. In the course of working out a method for measuring β-oxybutyric acid he became very bored setting up a battery of distilling flasks and then titrating the distillates. There was a bright 15-year-old Negro girl in the laboratory whose assignment was to wash the glassware. To our intense amusement McKim taught Topsy to perform this procedure and he boasted gleefully that none of 'you chemists' could measure so near the mark as Topsy.

"I must resist the temptation to further reminiscence of my years in this lush meadow of opportunity, else I will most certainly be felled by the gavel. They were filled with the pleasures of youthful enthusiasm and fine friendships."[2]

His first investigations were concerned with nitrogen metabolism in infants, but in 1920 he published a paper with Kenneth Blackfan, then finishing an 8-year stretch as Resident Physician at the Harriet Lane Home, which proved that infants synthesize cholesterol by demonstrating an excess of output of this substance over the amount taken in the diet. He then turned to a subject which occupied much of the rest of his

scientific career, namely acidosis. He seized upon one of the many "gifts of chance" to which he modestly ascribed his accomplishments, namely, the opportunity to study children being fasted for treatment of epilepsy. He carried out a classic study, which, characteristically, was not published until a year after he left Baltimore, on "The Metabolism of Fixed Base During Fasting." He describes the circumstances which permitted these studies as follows:

"The unusual opportunity to describe water and electrolyte balances and the processes of neutrality regulation under the stationary and simplified circumstances produced by absence of food intake was provided by a reported observation that the seizures of epilepsy disappear during fasting. Here the machination of fortune which gave us permission to fast children was a bit devious. The observation of the effect of fasting on epileptics had been made by a physical culturist who was not a physician. Obviously, however, it would be ungracious and absurd to ask for orthodoxy in the processes of chance. Indeed, I find in my Bartlett the statement that:

'Dame Fortune is a fickle gipsey
And always blind and sometimes tipsey.'

Perhaps you will say that is why we have been so companionable."[1]

Oscar Schloss of New York was appointed to Harvard's first full-time chair in pediatrics at the Children's Hospital in 1922. He had an unhappy year in Boston, as have so many pioneers of the full-time system, but he made two great contributions to the Harvard Medical School before resigning to resume his distinguished career in New York. First, he brought James Gamble to Boston and, second, he had the Laboratory Study building constructed at the Children's Hospital, thus making possible those studies of disease which influenced all of medicine so profoundly and providing for the training of a succession of clinical investigators, whose own contributions have pushed forward many medical frontiers. It is symptomatic of the period that the trustees of the hospital, like their counterparts elsewhere, had little enthusiasm for supporting laboratories from which the contributions to patient care were seldom immediately apparent. However, they finally agreed to finance the construction but charged the Medical School an annual rental, an arrangement terminated only a few years ago. The architects and builders of that period, likewise, were unfamiliar with laboratory construction and during the summer holidays quietly reversed Dr. Schloss's carefully thought out plans, thus exposing a generation of investigators, who were meant to labor on the north side of the building, to the heat and glare of a southern exposure.

From 1922, when he first came to Harvard as an Assistant Professor, until he became Professor Emeritus 28 years later, James Gamble fulfilled the role he had set for himself as a "student of disease using the methods of chemistry." At first, as he described it, "To my consternation Dr. Schloss returned to New York within a year and I

Fig. 1. James Gamble and Kenneth Blackfan stand in front of the Laboratory Study Building of the Children's Hospital, Boston. This picture was taken in the early years of their happy association there.

found myself . . . out on a limb, [but] my good luck held and my old friend Kenneth Blackfan came to Boston and presided over the Department with a splendid effectiveness for 18 years."[1] Allan Butler wrote, "the combination of Blackfan, the superb clinician and tactful administrator, and Gamble, the gifted investigator, each with full professorial rank, provided an unusual opportunity for both, as well as for all those who were fortunate enough to work under them."[3] No biographic memoir of Dr. Gamble would be complete without a tribute to Kenneth Blackfan, who provided the environment and personal support which permitted Gamble's genius to flower. During the happy days at Johns Hopkins, Blackfan's keen observations of the importance of dehydration in infantile diarrhea had provided the stimulus for much of Gamble's later work; subsequently, at the Children's Hospital from 1923 until Blackfan's death in 1941, they complemented one another in an extraordinarily complete and happy way. In Dr. Gamble's own words,

"A large cause of Kenneth Blackfan's success in leadership was his gentle friendliness. He always made his associates feel that they were his comrades in the enjoyable adventure against disease. Also he was very brave. Beginning in his latter Baltimore years, he suffered a series of physical afflictions which he bore with an unbelievable fortitude. He was friendly and gentle and brave. The simplicity and the sincerity of these traits gave him his great beauty of personality."[4]

At Harvard, Gamble's talents were soon recognized; he was named Associate Professor of Pediatrics in 1925 and became a full professor in 1932. His research moved forward from studies on the mechanism of acidosis to investigations of the effect of various lesions of the gastrointestinal tract upon the volume and composition of the body fluids. In 1933, with Allan Butler and Charles F. McKhann, he published an important paper entitled "Intracellular Fluid Loss in Diarrheal Disease," in which he pointed out the potassium deficits which his friend Daniel Darrow and his pupil Edward Pratt had the courage to repair with parenteral solutions in their important studies more than 10 years later. By 1939 he had assembled his observations and experiments in a loose-leaf syllabus, first privately printed and subsequently published by the Harvard Press, entitled "Chemical Anatomy, Physiology, and Pathology of Extracellular Fluid," which remains a medical classic and which has had a tremendous impact upon the thinking and practice of a whole generation of medical students and physicians.

The war period was a difficult one. Kenneth Blackfan died in 1941 at the age of 58. The tragedy of this loss was compounded for Dr. Gamble by his temporarily having to assume administrative responsibility for the Department at this most difficult time. Happily he was soon relieved of this uncongenial duty by the appointment of Richard Smith to Blackfan's chair in 1942. Dr. Gamble served his country well by collaborating in a study organized by Allan Butler at the Massachusetts General Hospital upon a group of conscientious objectors who voluntarily submitted themselves to conditions simulating those endured by survivors on a life raft at sea. From their self-imposed deprivations of food and water, from Dr. Butler's clear formulation of the physiologic problem, and from Dr. Gamble's careful analysis of the experimental data came much sound physiologic information, reported in a Harvey Lecture in 1946, which was not only applicable to promoting the survival of victims of bomber or U-boat but also to the treatment of fasting or anuric patients.

From 1941 to 1945 Dr. Gamble served as Editor of the *Journal of Clinical Investigation*. He maintained the high quality of this medical publication through the war period, initiated the custom of using a considerable number of the members of the "Young Turks" as reviewers, and published the first special numbers in which the results of certain of the major military medical research programs were brought together. He was much incensed when his request for extra paper to print these as supplements was turned down by the War Production Board, which still allowed the pharmaceutical firms

to turn out lush volumes of advertising literature for physicians.

After the war, a metabolism ward, something he had dreamed about for many years, was set up for him through the generosity of the Prouty family on Ward I Lower of the Children's Hospital. Here, with a group of younger colleagues led by William Wallace, he set about studying some of the inconsistencies of metabolic balance data, and, with the cooperation of a happy and tenderly cared for microcephalic baby named Billy, whose contributions to medicine still remain in Dr. Gamble's notebooks, he investigated some of the basic chemical phenomena of growth. Following his retirement in 1950, he continued to come to the hospital and to participate in the research of younger men by advising them, by carefully editing manuscripts, and by corresponding with those in other institutions who frequently sought his counsel by mail.

The direct impact of Dr. Gamble's research upon the development of medical thought has been momentous. Supportive therapy, whether given by pediatricians, internists, obstetricians, or surgeons, has been influenced by it for all time, and it would be impossible to say how many lives have been saved around the world because of his beautiful analyses of disturbances of the body fluids in disease states, his extraordinarily clear expositions of them through simple diagrams ("Gamblegrams"), and his lucid but arresting prose. His lectures and his writings, so easy to hear or read and so vividly phrased, were the product of anxious hours of laborious longhand composition. He labored over each lecture to the medical students, although he was thoroughly familiar with his topic. He strove for perfection, not only in the simple, decisive elegance of his experimental studies but in their presentation to others. His was no glib tongue or pen. From 1914, the year of his first publication, until 1955, his total bibliography includes only 51 papers, each of which is a masterpiece in content, in clarity of thought, and in felicity of style. His faculty for vivid, precise expression occasionally appears in the titles. For example, the Lane Medical Lectures given at Stanford in 1951 were entitled "The Companionship of Water and Electrolyte in the Organization of the Body Fluids" and his first Thayer Lecture at Johns Hopkins in 1937 was on "Extracellular Fluid and Its Vicissitudes."

Dr. Gamble's influence as a teacher was probably greatest through his writing. Despite extreme diffidence and dreadful anxiety before appearing on the platform, his lectures, which were illustrated by charts suspended from the carefully spaced hooks that were a feature of every Children's Hospital blackboard, were models of clarity. His anxiety led to a requirement for periodic sips of water taken from a laboratory beaker during the delivery of his lecture. At one of his final lectures at Harvard, a playful student replaced the water in the beaker with gin just before he entered the room. Dr. Gamble sipped its contents without any sign of surprise but at the end of his lecture broke his usual routine with a quick "bottoms up" amid thunderous applause from the admiring students.

In discussing his own career, Dr. Gamble frequently mentioned the good fortune which had made it possible for him to follow his own bent. He deplored the lack of sufficient funds which did not permit younger, less fortunate men to devote their lives to the study of disease in the laboratory. He was always interested in the "oncoming young men" who came to work with him and gave generously of his time, his thought, and often anonymously of his substance to help them. In Baltimore he had been one of a gay company of pioneers in pediatric research around Howland and Marriott. This spirit of freedom and informality made the laboratories at the Children's Hospital in Boston a happy place for his younger associates and for the small group of loyal and able technical assistants who worked with him. Here he became the leader of a laboratory through which, over a 30-year period, passed a small group of favored young men who felt the touch of his spirit and who carried it into medicine, surgery, and pediatrics in this and

many other countries. In Dallas, Chicago, Cleveland, Pittsburgh, Oklahoma City, Buffalo, New York, and Boston, and in Canada, Mexico, England, Denmark, Finland, France, Hungary, Turkey, and Indonesia, men holding important academic positions are carrying on their work with an inspiration which he provided by his own quiet, unassuming, but utterly honest example. This was no high-powered research institute but a training ground for clinical investigators where the future student of disease could learn by making his own measurements, by discussion with his associates, and by the final agonizing attempt to put his observations on paper in a manner that would necessitate less than three complete rewritings under Dr. Gamble's kindly but rigorous editorial scrutiny.

Although he was a shy man in a crowd of strangers, Dr. Gamble was a genial host in his home and a charming companion among his close associates. Not averse to the beverage which bears the name of his native Bourbon County and very fond of golf and sailing, he could enjoy life keenly with family and friends. It was proverbial that, in those happy Baltimore days and his earlier years in Boston, the expedition to the spring meetings at Atlantic City, with Dr. Gamble at the wheel of his old Cadillac, frequently got delayed at a golf club some miles short of its ultimate destination.

In 1916 he married Elisabeth Chafee of Providence. Her loyal devotion and warm, vivacious personality provided the essential complements to his own character and made theirs a very happy family. At their home in Brookline, their farm in Taunton, and their beautiful summer place in Sorrento, Maine, the Gambles have been very hospitable to friends and younger colleagues from this country and abroad who would find themselves swept into the activities of this large and charming family. Visitors to Sorrento would go sailing, golfing, swimming, or mountain climbing with children and parents and in the evening might be treated, if they were lucky, to a special showing of that motion picture classic, "Galahad and Vivian," in which the various members of the Gamble and Chafee tribe performed under his direction. In recent years, Dr. Gamble got the greatest pleasure out of his acquisition of Calf Island, formerly the summer camping ground of President Eliot and his children. Here he kept sheep and provided a haven of rest for weary young doctors and their families. He used to enjoy particularly the annual sheep shearing by Jennie Cirone, a sturdy citizen of Maine who directed the roundup and removed the wool with a manual dexterity he much admired. It is most appropriate that after the funeral service conducted by Dr. Gamble's neighbor at Sorrento, Rev. Henry P. Van Dusen, in the Harvard Church last May, his ashes were returned to his beloved Calf Island last summer at a simple service before family and friends. His wife, 5 children, and 16 grandchildren survive him.

Fig. 2. Dr. Gamble, in one of his last pictures, sits at the wheel of his yawl, *Torna a Sorrento*, in Frenchman's Bay, Maine.

Many honors came to Dr. Gamble in recognition of the importance of his work.

He received an honorary M.S. from Yale in 1930, M.D., from Zurich in 1950, and D.Sc. from Chicago in 1952. In 1946 he received the Borden Award of the American Academy of Pediatrics. He was given the Kober Medal of the Association of American Physicians in 1951 by Robert Loeb, the year after he had himself presented this award to his great friend, Edwards A. Park. These two men are the only pediatricians upon whom this honor has been bestowed. In April, 1955, the Royal College of Physicians of London awarded him their Moxon Medal, and in July of that same year at the Joint Meeting of the British, Canadian, and American Pediatric Societies in Quebec, he received the John Howland Award of the American Pediatric Society from his erstwhile pupil and long-time friend, Allan Butler. He was a Fellow of the American Academy of Arts and Sciences, and a member of the Interurban Clinical Club, the American Society for Clinical Investigation, the Association of American Physicians, the Society for Pediatric Research, and the American Pediatric Society, of which he was president in 1945. He was one of few pediatricians ever elected to the National Academy of Sciences.

He bore these honors lightly. His lasting influence stemmed from clarity of mind, warmth of friendly interest, simplicity of character, and gentle integrity which never frightened but always uplifted those whom he touched. As his great friend, Dr. A. N. Richards, put it, "There was not a spurious fibre in him."

CHARLES A. JANEWAY, M.D.

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Books

What Children Scribble and Why.

Rhoda Kellogg, Palo Alto, Calif., 1959, Nat. Press, 144 pages. Price $3.50.

This volume is of primary interest to educators and psychologists but is also of value to pediatricians who may be interested in aspects of the developmental sequence in children, specifically the sequences in scribbling and drawing. The author, an educator, has surveyed more than 100,000 drawings by children of nursery school age and developed a classificatory scheme. She describes the drawings in terms of an objective analysis of their order and sequence rather than a subjective interpretation of their psychological meaning. The survey is thorough and interesting.

WILLIAM J. MARK

Education for Child Rearing.

Orville G. Brim, Jr., New York, 1959, Russell Sage Foundation, 362 pages. Price $5.00.

This is a reference book that offers an over-all view on current thought and practice in parent education. As such it is more useful to the student of parent education than to the practitioner. Material is not presented to offer much concrete data to the person actively engaged in individual parent counseling, in leading a parent group, or in the preparation of mass media (lectures, publications, television, etc.).

On perusal of the book one may get the impression of considerable activity with not enough direction in the field of parent education. This impression is enhanced by the discussion on evaluation of programs. Attempts at evaluation generally are described as inconclusive. The lack of findings may be caused by the choice of study methods, which is always a problem in the behavioral sciences.

There is an interesting chapter on the history of education for child rearing. To the student of sociologic and psychological phenomena it emphasizes that, in contrast to popular belief, the task of raising children has always baffled parents and they have always had to look for information and support outside of the home.

HELEN L. BECK

Paediatrischer EKG Atlas.

Wilhelm Heck and Joachim Stoermer, Stuttgart, Germany, 1959, Georg Thieme, 200 pages. Price $18.55.

A pediatric EKG atlas is the missing link in the German literature on congenital heart disease.

In a short but comprehensive form the fundamentals of the EKG in infancy and childhood are reviewed and the vectorcardiogram is explained. The signs of left, right, and combined ventricular hypertrophy, so important in leading to the diagnosis of congenital malformations of the heart, are described clearly. The tables on the time intervals of the EKG in the different age groups in childhood are of precise value to the electrocardiographer.

A wide collection of EKG's covers all the varieties of congenital cardiac malformations. This collection is completed by the clinical, pathologic, and operative data of the described cases which are therefore explicit in themselves.

This atlas will be welcomed especially by the German-speaking physician and student interested in congenital heart disease.

PAUL GALL, M.D.
DAN G. MC NAMARA, M.D.

Neurology of Infancy.

Anatole Dekaban, M.D., Ph.D., Baltimore, 1959, Williams & Wilkins Company, 388 pages. Price $12.00.

This book is designed to acquaint the reader with various neurologic problems of infancy. The author discusses developmental landmarks in

normal full-term infants such as examination, birth injury, vascular disorders, infectious disease, dysrhaphic states, degenerative disease, and metabolic disorders.

Unfortunately, the author lacks a point of view, and the audience for whom the book is intended is not clear. The material is not substantially different from a textbook of pediatrics so that the contents are not likely to add to the knowledge of the medical student, the practicing pediatrician, or the general practitioner. It does not attempt to bridge the gap between a pediatric text and the fourth edition of the authoritative *Diseases of the Nervous System in Infancy, Childhood, and Adolescence* by Frank R. Ford by summarizing recent research or analyzing changing concepts. The neurologist or psychiatrist who sees adult patients primarily may find the various disease entities so simplified that he may be led to believe that problems of the younger age groups are miniature versions of those found in adults.

Part of the trouble lies in the inclusion of the effect of various disease processes in older children. Much of the text and many of the illustrations are devoted to patients more than 2 years of age. One learns, for example, that Sydenham's chorea is rare in infants. No doubt this is an understatement, but almost a page is devoted to the condition.

Specific objections are found easily. Prematurity is not listed in the index and virtually is omitted in the text. The possible effects of prematurity, nutrition, or social deprivation are not discussed on the rather elaborate developmental tables. One learns from the tables that the 2-month-old infant voids approximately 20 times each 24 hours, the 3-month-old 18 times, the 7- to 8-month-old 16 times, and the 9- to 10-month-old 14 times. Nothing appears in the text to explain what purpose, if any, this information might serve, what variation might be expected, or from what source it is derived.

Nothing is given on the treatment of hypernatremia or on the infant of the diabetic mother. Aldosteronism is said to occur during infancy, but the reference cited concerns a 9-year-old child. The material concerning amaurotic familial idiocy (Tay-Sachs disease) indicates that the defect is in the accumulation of a ganglioside, not a sphingomyelin. Cross references and a meaningful index are lacking. For example, a short paragraph on the autonomic nervous system (p. 64) states that dysautlonomia (sic dysautonomia) is a serious condition. It is listed in the index under "familial" and is discussed later in the text under "familial dysautonomia" (p. 261). The discussion is primarily about older children but includes a paragraph on the condition in infants. For example, corneal ulceration in patients under 1 year of age is observed quite frequently, according to the text, but the child in the photograph which illustrates the point appears to be at least 4 years of age.

The bibliography is adequate and is recommended as a supplement to Ford's fourth edition.

HENRY W. BAIRD, III, M.D.

Premature Infants, Their Nursing Care and Management.

A. K. Geddes, M.D., Philadelphia, 1960, W. B. Saunders Company, 215 pages. Price $4.50.

General principles of nursing care for premature infants, details of technique and management, and basic attitudes toward the immature baby are presented well in this small book. The writing is lucid and largely unencumbered by lengthy discussions of medical management. However, the medical aspects are mentioned briefly in a helpful way to give the nurse some necessary understanding of pediatric care. The premature infant is defined as one weighing less than 5 pounds at birth, rather than the usual statistical division at 2,500 grams or 5½ pounds. In dealing with newborn infants, one would welcome a complete change to the greater simplicity of the metric system for weights and volumes. Minor differences of opinion concerning medical recommendations do not interfere with the usefulness of the book for nurses. The maximal dose of chloramphenicol is given as 50 mg. per kilogram per day. Perhaps half of this might be safer for premature infants. Schools of nursing should find the book useful, and a copy might well be left in the premature nursery.

F. H. HARVIE, M.D.

News and notes

The Children's Hospital of Philadelphia and the Graduate School of Medicine, University of Pennsylvania, announce **courses on Pediatric Advances,** May 30 to June 3, and on **Practical Pediatric Hematology,** June 6 to 10.

Pediatric Advances will consist of clinics, demonstrations, and panel discussions in selected aspects of contemporary pediatrics. Total attendance is limited. Tuition is $115.00.

Practical Pediatric Hematology, will be conducted by Irving J. Wolman, M.D., Thomas R. Boggs, Jr., M.D., and other members of the Hematology Department of The Children's Hospital of Philadelphia. Tuition is $125.00. The last two days will be devoted to problems of blood grouping, neonatal jaundice, kernicterus, and exchange transfusions. Tuition for these two days only is $50.00.

A collection of 25 slides on abnormal blood and bone marrow has been prepared for purchase at $10.00 by registrants and at $15.00 by nonregistrants.

For information write to Irving J. Wolman, M.D., Director of Postgraduate Education, The Children's Hospital of Philadelphia, 1740 Bainbridge Street, Philadelphia 46, Pa.

The **Eighth Annual Clifford D. Sweet Seminar of Children's Hospital of the East Bay, Oakland, California,** will be held June 2 to 4. Participants will include Drs. Robert A. Aldrich, James L. Dennis, Lytt I. Gardner, Robert A. Good, Arild E. Hansen, and Irvine McQuarrie.

For further information write to Children's Hospital of the East Bay, 51st and Grove Streets, Oakland, Calif.

Dr. Henry G. Cramblett, former Assistant Professor of Pediatrics at the State University of Iowa Medical School, has accepted the position of Associate Professor of Pediatrics at the Bowman Gray School of Medicine of Wake Forest College. He will also serve as director of a new department known as the Virology Laboratories.

In their first bulletin, the Organization Committee of the **X International Congress of Pediatrics,** composed of Drs. Carlos Salazar de Sousa, José dos Santos Bessa, Mário Cordeiro, and Silva Nunes, has outlined initial plans for the Congress. Registration for the Congress, to be held Sept. 9 to 15, 1962, at the University City of Lisbon, will begin Aug. 1, 1961. There will be 3 plenary sessions the first 3 mornings during which there will be no group sessions. Simultaneous sessions on general and specific subjects will be held during the remaining time. Official languages will be Portuguese, French, and English.

There will be an official banquet and dance, an old-fashioned Portuguese bullfight, and a dinner in a "typical" Portuguese restaurant where the "Fado" will be sung. Among other Congress tours now being planned, will be one to Madeira.

"Causes of Mental Retardation and Practical Approach to Diagnosis and Management" will be the title of the postgraduate symposium to be held June 2 to 4 at the Texas Children's Hospital, Houston. It will be sponsored by The Department of Pediatrics, Baylor University College of Medicine, and The Division of Maternal and Child Health, State of Texas Department of Health.

EDITOR'S COLUMN

The magic of numbers—"20 milligrams of bilirubin"

THAT kernicterus is related directly to hyperbilirubinemia has been established unequivocally. Although susceptibility varies, the likelihood of this complication in the infant affected by erythroblastosis when the indirect bilirubin concentration is in the range of 18 to 20 mg. per cent has been documented fully. The emphasis on maintaining serum bilirubin levels below 20 mg. by one or more exchange transfusions has led to a truly remarkable reduction in damage to the nervous system.

It was not to be expected, however, that all the complexities of erythroblastosis relative to the precise timing of every exchange transfusion could be resolved, because so many individual factors enter into a decision. Examples of these perplexing situations include the advisability of exchange transfusion in the small, premature infant, the number of re-exchanges in a patient with resurging hyperbilirubinemia, and the need, if at all, for extending treatment into the second week of life. Particularly distressing are those circumstances involving ABO incompatibility which unexpectedly confront the pediatrician on the fourth or fifth day of the infant's life. Such an infant is usually first born and appears otherwise healthy, with a normal concentration of hemoglobin, a negative Coombs test, and an indirect serum bilirubin level approximating 20 mg. per 100 ml. Consultation at this juncture usually produces divergent opinions: whether to postpone a decision for 24 hours, to use 21 to 23 mg. as a guide, or to exchange immediately.

What has been more harassing in recent years is the management of the infant with hyperbilirubinemia without blood group incompatibility, a condition attributed to an exaggeration of physiologic icterus. In a few infants this elevation has been shown to be due to an excessive dosage of vitamin K. In the majority of infants, however, excessive levels of indirect serum bilirubin develop spontaneously, especially in the premature ones. It would be expected, since this indirect bilirubin is presumably comparable to what accumulates in hemolytic disease of the newborn, that the same attitude toward exchange transfusions should prevail in both, because of the likelihood of damage to the nerve cell with levels above 20 mg. of indirect bilirubin. As stated, the problem is particularly acute in the premature and to a lesser extent in the full-term infant.

In this group of cases there are conflicting views as to the critical levels for exchange transfusions, or even for their routine use. Grosse and colleagues[1] emphasize that replacement should be performed promptly in premature infants if the serum level of indirect bilirubin is over 18 mg. per 100 ml. or at a lower level if the bilirubin is rising rapidly. Newns and Norron[2] would give transfusions to those infants with a serum bilirubin level of 30 mg. and below "if they become lethargic, irritable, difficult to feed, or if there is a rapid rise of serum bilirubin on the third or fourth day." On the other hand, Holman[3] claims that "because of the variability of concentration of bilirubin in the plasma of premature infants and because of the multitude of factors that play a possible role in determining the ultimate concentration of bilirubin, routine exchange transfusion for elevated concentrations of

bilirubin does not seem warranted." This view has been challenged vigorously[4] with the criticism that such a policy might undermine the progress made in preventing damage to the nervous system. After reviewing their cases of hyperbilirubinemia without blood group incompatibility, Mores and coworkers[5] claim that "prophylactic exchange transfusion in full-term infants is useless; in premature infants it is theoretically unfounded and its practical value has not been proven, not even by those performing it." In contrast with this statement, Meyer[6] cautions that there might even be justification for replacement transfusion with a rapidly rising bilirubin before levels of 18 and 20 mg. are reached. It should again be emphasized that at present there is no unanimity of opinion with regard to management of these cases. In general, the trend seems to be to give exchange transfusions to affected infants with the reservation that critical levels cannot be stated categorically. Thus one must still lean on the 20 mg. bilirubin level of the infant affected by erythroblastosis for guidance.[7]

In this dilemma, especially in nonerythroblastotic hyperbilirubinemia, since exchange transfusion per se involves a definite risk, it would seem advisable to give the pediatrician some leeway in making his own decision as to treatment. He must of course apprise himself of all the facts and if necessary seek further consultation. The consensus in the situations enumerated in both erythroblastic and nonerythroblastic jaundice is that the physician must be guided by judgment based on evaluation of the essential data in the individual case rather than on blind adherence to an inflexible yardstick. This freedom of action, however, necessitates operation without the fear of litigation in the event of involvement of the nervous system. It is essential, therefore, in this state of incomplete information, for an authoritative body to support and protect the pediatrician by a statement of policy outlining the circumstances under which the 20 mg. bilirubin level can be relaxed.

In no way are these comments to be interpreted as a disparagement of the standards which experience has demonstrated to have been so effective in preventing and reducing the incidence of kernicterus; rather, they are to implement what has already been established by the accumulation of additional data in an unharried atmosphere.

CARL H. SMITH, M.D.

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Early delivery for hemolytic disease of the newborn?

IT BECAME evident about a decade ago that a single exchange transfusion prevented kernicterus in some infants with hemolytic disease, that prematurely born infants were in greater risk of kernicterus, and that a single exchange transfusion left the incidence of kernicterus in such infants uncomfortably high (14 per cent in infants delivered before

38 weeks' calculated gestation).[1] More recently, with advances in understanding of the relationship of kernicterus to the level of serum bilirubin, realization has come that where multiple exchange transfusions can be used in such a way as to keep the level of serum bilirubin below some critical point, kernicterus does not occur. Since today most deaths due to hemolytic disease occur in utero and can be prevented only by early delivery of the infant, there has been a new movement of the pendulum, which 10 years ago swung strongly away from early interruption of pregnancy as an aid in management of hemolytic disease of the newborn. The re-evaluation of the proper role of early delivery in improving the prognosis for the potentially affected infant has been set in motion by Chown,[2] Allen,[3] Walker,[4] Tovey,[5] and others.[6]

It is evident that gains to be made through early interruption of pregnancy are limited at the outset by the fact that fetal death, as Allen[3] and Walker and associates[4] have shown, occurs as early as 32 to 33 weeks' gestation in perhaps as many as a third of infants in whom death will occur in utero and that the attempt to forestall such ante-partum death through ever earlier interruption of pregnancy must ultimately fail as a result of rising mortality due to prematurity alone, even if it were possible to manage adequately hemolytic disease in such infants through multiple exchange transfusions. It is generally agreed that the woman whose infant is at highest risk of being stillborn is the one who previously has been delivered of a stillborn child and that the risk increases with each successive stillbirth. Moreover, the times of intrauterine death may, in some instances, be earlier with each successive infant, though variability and unpredictability are to be expected here. It seems necessary, in any case, to aim at a fairly early point in the last trimester of pregnancy for the delivery of certain sensitized women who have homozygous husbands.

Chown[2] would reserve interruption of pregnancy for mothers who previously have given birth to stillborn infants, except that he would also consider the interruption of pregnancy in a mother who had shown a fourfold rise in antibody titer during pregnancy and whose husband is homozygous. Inferences drawn from changes in titer during pregnancy are generally likely to be found, from a prognostic standpoint, much less helpful than history of the degree of illness in previously affected infants. Kelsall, Vos, and Kirk[6] suggest, and Tovey and Valaes[5] concur, that the level of maternal antibody as determined by antiglobulin technique has a better correlation with prognosis than other determinations, but they point out that special pains are necessary in order to assure the reproducibility of antiglobulin titer. It is not clear, however, that other laboratories will be able to use this titer with the same level of confidence which these workers enjoy. Moreover, it is inherently unlikely that maternal titer, however measured, should select accurately those infants in need of early termination of intrauterine stay, since fetuses differ in their responses to identical levels of maternal antibody. This is best demonstrated in dizygous twins, in whom one Rh-positive twin may be affected substantially more than the other.[7] Undoubtedly many other factors besides maternal titer contribute to the risk to the infant at each point in pregnancy.

When the decision is made that early interruption of pregnancy is appropriate in the hope of forestalling stillbirth, there will still be uncertainty as to the choice of time. Chown and colleagues[2] have induced labor as early as 32 weeks, but apparently have no fixed policy. Walker[4] has suggested that labor might well be induced at 35 weeks' pregnancy in mothers with a history of one stillbirth or of a severely affected child and at 32 weeks' in mothers with 2 previous stillbirths. It seems probable that at present no better index than history exists for determining the time of delivery, though somewhat arbitrary use of such an index will often be necessary. Other possibilities have been explored and deserve further study. Bevis[8] has examined specimens of amniotic fluid, taken

at weekly or biweekly intervals in the last trimester of pregnancy, in the hope that pigmentary or other changes might reflect accurately the condition of the infant. His earliest observations were encouraging. Chown, on the other hand, feels that he may have seen an abrupt rise in antibody titer following paracentesis in which it is probable that an injury to the placenta occurred which permitted fetal blood to enter the maternal circulation. Others have observed, and we can confirm, that many mothers about to give birth to a stillborn infant, will, before the death of the fetus occurs in utero, undergo a few days' subjective distress which seems to be related to the rapidly worsening illness in the baby. Such mothers have the feeling that the uterus is rapidly enlarging and will sense pressure and discomfort, even when, sometimes, it is not possible to find convincing reason for this on external examination. At about this time the fetus often becomes less active. It is our feeling that when these signs have appeared, the fetus is in serious danger, if not already beyond help. The occurrence and adequate evaluation of these signs and symptoms in a mother who has had a previous pregnancy which terminated in delivery of a severely ill or dead infant may suggest that the early delivery of the baby is imperative. Needless to say, vague anxiety that the infant might be less active, or other vague complaints in a mother looking anxiously for signs of difficulty, should not be taken too hastily to mean that the infant is in trouble.

Both Chown and Walker prefer vaginal delivery in the sensitized mother even when labor is induced surgically very early and suggest reserving cesarean section for failures of adequate induction of labor. This preference may be underscored by Allen's lack of favorable issue in infants delivered at 35 weeks by hysterotomy.

While there seems to be no doubt that interruption of pregnancy in the sensitized mother as early as 32 to 35 weeks' gestation should be reserved for those situations in which the risk of a stillbirth is high, there may be other cogent reasons, as Allen has pointed out, for *planned* and often early delivery of sensitized mothers in whom the prognosis for the infant seems good, though at a time closer to the expected date of confinement. Allen has suggested that *all* sensitized women ought to be considered candidates for delivery as soon as they reach 37 to 38 weeks' gestation and are found obstetrically favorable for induction of labor. He points out that under the circumstances of planned delivery it is possible for a hospital to be forewarned that there will be special demands upon the blood bank and clinical laboratory during a certain period and to be assured that those who will be responsible for care of the infant will be able to arrange their affairs in such a way as to leave them free for whatever demands the infant may make for energetic therapy. Any advantage to such a program beyond the occasional prevention of a stillbirth which might occur at a later point in pregnancy may depend heavily upon the adequacy of local facilities and the manner in which they are used.

A strong argument can be made for the centralization of care of sensitized mothers in institutions where the necessary facilities and experience with transfusion techniques are available. The larger the number of cases that such areas are able to supervise, the more rapidly we will learn how best to fit the interruption of pregnancy into the pattern of care of the sensitized woman and her baby.

It goes without saying that whenever delivery of the sensitized mother is contemplated or carried out, it is imperative that adequate facilities be at hand for the performance of multiple exchange transfusions and for the accurate determination of levels of serum bilirubin on short notice at all hours of the day and night.

As further experience with interruption of pregnancy in the care of the sensitized mother becomes available, it will be of the greatest interest to see where the moving pendulum comes to rest. That it will stay at rest for long is doubtful, since it is not

to be expected that interruption of pregnancy will prove to be the final answer to the problem of stillbirth in hemolytic disease. Some other measure will be necessary for the support of the infant in utero who will succumb prior to the time when early delivery might save him. It remains to be seen whether measures developed for the support of the infant in utero ultimately may permit survival to term. At present no known drug or nutritional supplement seems to offer that hope.

VICTOR C. VAUGHAN, III, M.D.

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Erratum. *In the article, by Vietti and others, "Observations on the Prophylactic Use of Vitamin K in the Newborn Infant," in the March, 1960, issue of the* JOURNAL, *the sentence beginning on line 10 of the second column on page 344 should read as follows: "One of the 6 babies who received vitamin K, and 14 of the 32 babies who had not, required resuturing of the circumcision."*